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SUDDEN AND UNEXPECTED DEATHS OF YOUNG SOLDIERS

Diseases Responsible for Such Deaths During World War II

ALAN R. MORITZ, M.D.
Professor of Legal Medicine, Harvard Medical School
BOSTON
AND
CAPTAIN NORMAN ZAMCHECK *
MEDICAL CORPS, ARMY OF THE UNITED STATES

AMONG the more than 40,000 autopsy protocols that were received at the Army Institute of Pathology between January 1942 and January 1946, there were many which concerned young and apparently healthy soldiers whose collapse and death from disease were so sudden and unexpected that there was little or no opportunity to make an antemortem diagnosis.

For several reasons this group of deaths was thought to provide a unique opportunity to study the kinds and special characteristics of those diseases which, by reason of either rapid evolution or sudden transformation of a latent abnormality into one incompatible with continued life, were most frequently responsible for the unexpected deaths of apparently healthy young adults.

One of the principal reasons for regarding the source material as unique was the fact that there was relatively little opportunity for a sick or indisposed soldier to escape medical surveillance for long in the military installations in continental United States, from which the majority of these deaths were reported. Although dispensary and hospital facilities were readily accessible, relatively few of these men had sought medical attention before their fatal seizure. Most of them either thought themselves to be in good health or were remarkably reticent about their ill health. It could be assumed that the majority had recently passed one or more complete physical examinations incident to induction into the Army, in the process of which neither a real nor a potential threat to health was recognized. It is difficult to see how a comparable series of cases could be collected from civilian sources.

From the Army Institute of Pathology, Washington, D. C.
* From the Department of Legal Medicine, Harvard Medical School.

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The academic interest inherent in a study of sudden death from such well controlled source material is at once apparent, and there is also the possibility of obtaining practical information of military significance from such an investigation. It might be found that certain causes of unexpected death are peculiar to camp or barrack life. It might be disclosed that certain apparently insignificant prodromal disturbances had actually given warning of the impending disaster. Evidence might be adduced that certain physical or constitutional types are more susceptible than others to the kinds of degenerative disease or structural defects responsible for unexpected death. An answer might be suggested to the important question of whether or not there is a cause and effect relationship between strenuous physical exertion and death from disease.

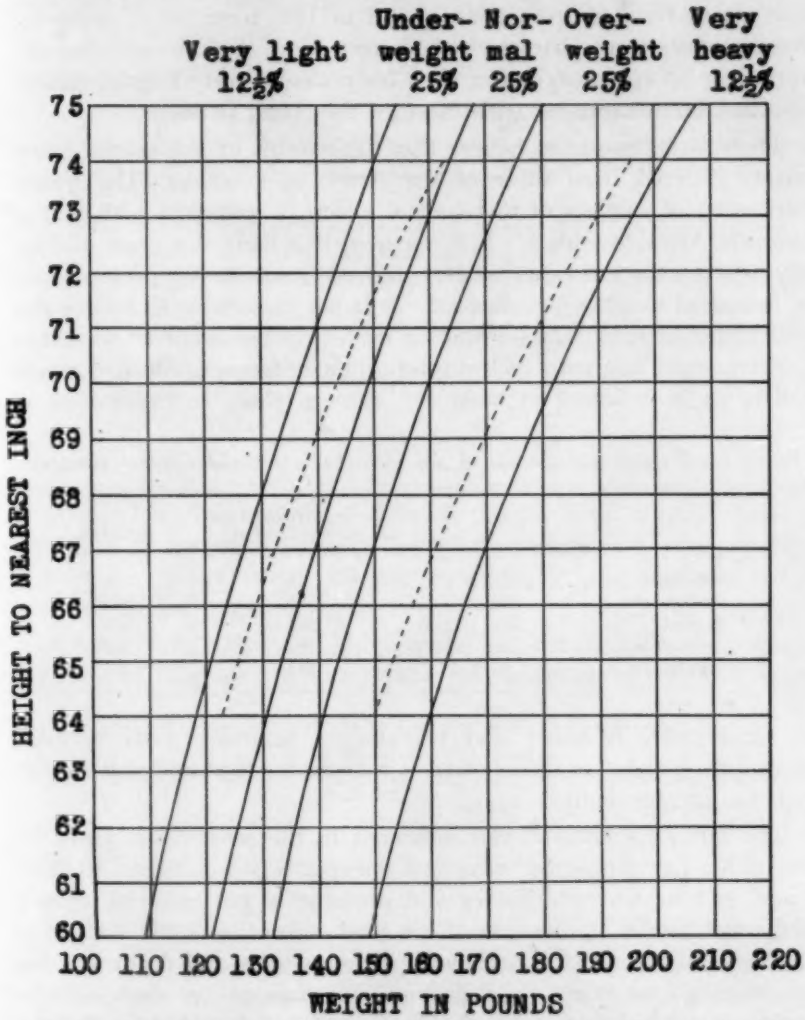
It soon became apparent that there were certain almost insurmountable difficulties to the making of a comprehensive statistical investigation of all causes of sudden death. One obstacle was the lack of uniform criteria for the determination of what constituted "sudden death." Therefore, to ascertain that this study included all deaths which had occurred within twenty-four hours after the onset of incapacitating symptoms would have required the reexamination of practically all protocols that had been received over this period. The alternative elected was to determine the various diseases that were responsible for unexpected deaths and then to investigate in some detail the diseases most commonly implicated.

Early in the investigation it became apparent that the body weight of many of those who died unexpectedly from disease was greater than that of the average soldier. In order to determine the extent to which the body weight in various categories of unexpected death deviated from the average, information pertaining to the stature and the body weight of all inductees was obtained through the statistical department of the Office of the Surgeon General.

The percentile distribution of all inductees in relation to body weight and stature is shown in the chart. The weight range of the 25 per cent of all soldiers that was central will hereafter be designated as "normal." The weight range that included the next 25 per cent of all soldiers that were heavier than "normal" will be designated as "overweight," and the next 25 per cent that were lighter than "normal" as "underweight." The extremes, which included the heaviest and lightest 12.5 per cent of all soldiers, will be referred to as "very heavy" and "very light." The Army's data on weight and stature of inductees correspond closely to statistics issued by the Metropolitan Life Insurance Company [1] for men over 25 years of age. The upper and lower

1. Ideal Weights for Men, Statist. Bull. Metrop. Life Insur. Co. **24**:6 (June) 1943.

limits of the ideal weight range for civilian men are indicated by the dotted lines in the chart. Whereas the Army has designated the central 25 per cent of inductees as normal, approximately 40 per cent of them fall within the "ideal" weight range for civilians.



The solid lines indicate the percentile distribution of all inductees during World War II according to weight and stature. The interrupted lines indicate the upper and lower limits for ideal weight according to stature of men over 25 as published by the Metropolitan Life Insurance Company.

The principal difficulty involved in interpreting the relationship of the data on weight to the incidence of disease is in the obtaining of accurate data at the autopsy table. Since these weights are largely estimates rather than true measurements, a sizable error may arise, obscuring such relationships as may exist.

In order to determine the extent to which autopsy room estimates of weight correspond with the measured weights of living soldiers, an analysis was made of data derived from the autopsy protocols of 296 soldiers who died of immediately fatal accidental injuries. In 180 of these, death resulted from gunfire, and in 116, from traffic accidents. These soldiers were characterized as very light, underweight, normal, overweight or very heavy after their body weight–body length relationships had been compared with those of the Army at large.

There is no reason to believe that the weights of this special group actually differed from those of the Army as a whole. The weight distribution of soldiers of this control group is compared with that of the entire Army in table 1. It is apparent that there is a great discrepancy between the estimated weights derived from autopsy protocols and the measured weights of inductees. It is not reasonable to believe that accidentally incurred fatal gunshot or traffic injuries occurred so seldom in underweight and with such disproportionate frequency in overweight soldiers as is indicated in table 1. A more plausible explanation of

TABLE 1.—*Weight Distribution of Soldiers (Inductees and Control Groups)*

Weight	Control Group of 296 Soldiers Dead of Accidents, per Cent	Inductees, per Cent
Very light	3.5	12.5
Underweight	10.5	25.0
Normal	23.0	25.0
Overweight	42.6	25.0
Very heavy	20.4	12.5

this discrepancy is either that pathologists habitually tend to overestimate the weights of dead bodies or that the average soldier is heavier than the average inductee.

The following criteria were observed in the selection of cases for this study: (*a*) the soldier who died unexpectedly was under 40 years of age, (*b*) he was ambulatory and presumably not suffering from a dangerous disease at the time of his fatal seizure, (*c*) the interval of time between the onset of incapacitating symptoms and death was less than twenty-four hours, (*d*) postmortem examination disclosed that death had resulted from recognizable disease or (*e*) that the pathologic changes were inadequate to account for death (excluding those cases in which trauma and poisoning, including alcohol, were considered probable because of anamnestic information and/or toxicologic analyses).

It was discovered that the principal categories of disease responsible for sudden death were heart disease, intracranial hemorrhage, meningococcemia, miscellaneous diseases and cause of death not disclosed by autopsy.

HEART DISEASE

Organic heart disease was estimated to have been responsible for between 200 and 300 unexpected deaths.[2] It was estimated that more than 200 of these were due to coronary arteriosclerosis and at least 34 to other cardiac diseases.

Coronary Arteriosclerosis.

A group of 115 unexpected deaths from disease of the coronary arteries was selected for study, in the belief that it constituted a representative sample of deaths from this cause.

TABLE 2.—*Age Distribution in Cases of Sudden Death from Coronary Arteriosclerosis*

Age, Years	Unexpected Deaths from Coronary Disease, per Cent	Total Army Personnel, per Cent
Under 20	0	9
20-24	8	38
25-29	14	30
30-34	44	16
35-39	34	6

Age.—The distribution of sudden deaths from coronary disease according to age in relation to that of the Army as a whole is given in table 2. It is apparent that the incidence of fatal coronary disease rises rapidly with age.

Race.—Only 6 of the 115 unexpected deaths from this disease occurred in Negroes. Although the total number is relatively small,

TABLE 3.—*Weight Distribution in Cases of Sudden Death from Coronary Arteriosclerosis (92 Cases)*

Weight	Sudden Coronary Deaths, per Cent	Accidental Deaths, per Cent
Very light	2.9	3.5
Underweight	16.0	10.5
Normal	17.0	23.0
Overweight	41.0	42.6
Very heavy	23.0	20.4

since the ratio of Negroes to white persons in the Army was approximately 1:9, this may provide some indication of a lesser susceptibility of Negroes to sudden death from disease of the coronary arteries.

Obesity.—The relation of body weight to unexpected death from coronary disease is given in table 3. It appears that the incidence of obesity as based on autopsy room estimates of weight is no higher in

2. A complete study of deaths from disease of the coronary arteries in soldiers aged 20 to 39 is being prepared by Dr. Wallace Yater, civilian consultant to the Army Institute of Pathology, and associates.

soldiers dead of coronary disease than in those dead of accidental mechanical violence.

Exertion.—In 98 instances the type of physical activity that had preceded or accompanied the onset of the fatal seizure was recorded. The relation of physical exertion to death from coronary disease is shown in table 4.

If the onset of acute heart failure due to coronary insufficiency were unrelated to any extrinsic factor, the incidence during any given interval of time throughout the day or the night should be proportional to the duration of that interval. If such were the case and if the soldiers spent an average of one third of their time sleeping, it might be expected that the onset of acute heart failure would have taken place during sleep in approximately one third of the deaths. It may be seen that the onset of acute heart failure occurred during sleep in only 15 per cent of the cases. In 29 per cent the onset of heart failure coincided with or immediately followed strenuous physical exertion. If the estimate

TABLE 4.—*Relationship of Physical Activity to Onset of Fatal Seizure (98 Cases)*

Type of Activity	Estimated Time Devoted by Soldier to Inactivity and to Activity, per Cent	Fatal Seizures Coincident with Inactivity or Activity, per Cent
Sleep	33	15
Inactivity—subject awake	17	21
Ordinary activity	33	35
Strenuous exertion	17	29

is correct that not more than 17 per cent of the average soldier's twenty-four hour day was devoted to strenuous physical activity, it appears that the number of those whose fatal seizures occurred incident to exertion was in excess of that which would be expected by random distribution. It is not likely that all cases in which the onset of acute heart failure was related to physical exertion are actually included in this 29 per cent. It could not be determined how many of those who collapsed during rest or during ordinary activity had become recently inactive or less active because of increasing physical disability. Thus there were a number of instances in which a soldier found dead in bed was reported as having been "below par" or "not feeling well" on the previous day. Usually such a record did not indicate whether the initial indisposition occurred during rest or during a period of unusual physical exertion. Thus, although the onset of the attack in 29 per cent of the cases of unexpected death from coronary disease was known to be related to exercise, the actual coincidence may have been considerably greater.

It is recognized that data of this kind do not prove or disprove a cause and effect relationship between physical activity and acute heart

failure. However, they do suggest that if a young man is to die unexpectedly of coronary disease, the onset of the terminal attack of acute heart failure is more likely to take place during strenuous physical exertion than during sleep.

Survival Time After Onset of Fatal Seizure.—In 75 instances it was explicity stated that death occurred within a few minutes or less after the onset of incapacitating symptoms. These represented soldiers who were regarded as healthy or at least as not dangerously ill until a few minutes before death. In 20 instances the onset of incapacitating symptoms was survived for periods that ranged between fifteen minutes and twenty-four hours. There were 20 soldiers who were found dead in circumstances that made it impossible to estimate the exact interval between fatal seizure and death, although it was known to be less than twenty-four hours.

Nature of Fatal Seizure.—The precise nature of the fatal seizure was either unknown or not recorded in 27 instances. In 42 it consisted in an unexpected syncopal attack; if there were prodromal symptoms, they were either not recorded or not complained of. In 2, convulsions followed loss of consciousness. In 44 instances the soldier complained of pain (precordial or epigastric) or both pain and vomiting immediately before loss of consciousness.

Past History.—As previously indicated, these 115 instances represented cases of unexpected death of a soldier who, so far as could be learned, was not recognized to be suffering from coronary disease. In 94 cases, the patient thought that he had been well prior to the time of his fatal seizure, he had not complained or information regarding his previous symptoms was not recorded in the history of the case. In 21 there was a record of previous symptoms which in retrospect could be attributed to coronary disease. Nineteen soldiers had suffered previous attacks of precordial or epigastric pain, the latter sometimes being regarded as indigestion. Three of these soldiers were also known to have complained of shortness of breath or excessive fatigability. Two, who had apparently not complained of previous attacks of pain, had a history of fainting spells on one or more occasions.

Pathologic Observations.—In each of the 115 cases gross and microscopic examinations of the heart and other organs were made. In all instances the descriptions indicated that one or both coronary arteries were the seat of severe atherosclerosis. The sclerotic changes involved the main arterial trunks in all but 2 cases, and in these the disease was described as affecting principally the small, intramuscular branches of the arteries. So far as could be determined from the protocols, the vascular lesions did not differ significantly from those observed in the coronary arteries of older persons, except that there was less calcifica-

tion. Although subintimal hemorrhage was observed in several instances, occlusion of the lumen by this cause was not described. In some the vessels were described as obliterated by sclerotic change, and in others the diseased vessels were occluded by thrombi. The principal pathologic characteristics of this group are summarized in table 5.

It may be seen in table 5 that in approximately half of the cases complete occlusion of a coronary artery was not found and that in less than a third was thrombosis demonstrated. The finding that the ratio of left to right coronary occlusion is approximately 2.5 : 1 is in general accord with the observations of others.

It is of interest that myocardial infarction was found in less than a fifth of these cases.

TABLE 5.—*Pathologic Changes Observed in 115 Cases of Sudden Death from Coronary Arteriosclerosis*

Pathologic Change Observed at Autopsy		
Coronary thrombosis	31	
Left	24	
Right	7	
Obliterative coronary arteriosclerosis (without recognized thrombosis)	23	
Left	14	
Right	9	
Severe coronary arteriosclerosis (neither thrombosis nor obliteration observed)	61	
Total		115
Myocardial infarction	22	
Recent	15	
Healed	7	
Myocardial fibrosis without recognized infarction	27	
No mention of myocardial pathologic change	66	
Total		115
Cardiac hypertrophy		
Heart weight known or inferred to be less than 400 Gm.	82	
Heart weight over 400 Gm.	33	
Total		115

In 82 instances the heart weight either was recorded to be less than 400 Gm. or could be inferred to be from the description. In only 2 instances was the heart weight reported in excess of 450 Gm.

Characteristically the lungs and the abdominal organs were described as being the seat of acute passive hyperemia. Although heavy lungs were almost invariably observed when the interval between collapse and death had been longer than a few minutes, there were a number of instances in which severe pulmonary edema was observed in a soldier whose collapse and death were described as almost instantaneous.

Although no attempt was made to review all the histologic material, random sampling confirmed the observations of Allen [3] in regard to the high frequency of splenic eosinophilia in cases of sudden death.

In 4 instances of sudden death from coronary disease there was both gross and microscopic evidence of agonal or postmortem bleeding

3. Allen, A. C.: Arch. Path. **37**:20, 1944.

throughout the head and body of the pancreas. In 1 of these, death had occurred within a few minutes after the onset of the fatal seizure. There was no apparent relationship between the presence of pancreatic hemorrhage and the length of the interval between death and postmortem examination.

Other Forms of Heart Disease.

There were 34 cases in which death was due to some form of heart disease other than coronary arteriosclerosis. These fell into the following categories:

Acute and Subacute Isolated Myocarditis.—In 14 instances death of acute heart failure resulted from diffuse or focal exudative inflammation of the myocardium. The ages of the subjects ranged between 18 and 36 years; 12 were white, and 2 were Negroes. Ten of the 14 died within a few minutes after an unexpected syncopal attack.

In 2 soldiers the fatal seizure occurred during a period of strenuous physical exertion, and 8 were at rest or engaged in ordinary activity. Four were found dead in bed. Five of the 14 were reported to have been below par for a day or so prior to the occurrence of the fatal seizure, although none had been confined to bed. The records did not indicate that any of the 14 recently had been hospitalized or had suffered from an infectious disease more serious than a cold. Postmortem examinations were reported to have disclosed no significant pathologic changes other than myocarditis.

Syphilitic Aortitis.—In 6 cases of sudden death active syphilitic inflammation of the aortic ring was found at postmortem examination. In 3 there was complete occlusion of a coronary ostium, in 1 a nondeforming aortic valvulitis and in another aortitis with dilatation of the aortic ring. All 6 of the soldiers were over 30 years of age; 4 were Negroes and 2 were white persons. None of them was known to have complained of not feeling well prior to the time of the fatal seizure. Two were found dead in bed, and the other 4 died within a few minutes after unexpected syncopal attacks which occurred during periods of ordinary activity. None of the protocols contained a description of any lesion that could be construed as syphilitic myocarditis.

Rheumatic Heart Disease.—The unexpected deaths of 5 soldiers were attributed to rheumatic heart disease. Acute cardiac dilatation was found in all 5, but only one heart weighed more than 400 Gm. Chronic valvulitis was present in all 5, but in only 1 was significant valvular deformity (mitral stenosis) described. In 1 of the 5 the microscopic observations indicated active rheumatic carditis. One was found dead in bed, and the other 4 collapsed unexpectedly during periods of physical exertion.

Idiopathic Myocardial Fibrosis.—Five deaths were attributed to acute cardiac failure due to extensive myocardial fibrosis which was not associated with coronary disease, exudative myocarditis or recognizable rheumatic stigmas. In 3 of the 5 cases there was cardiac hypertrophy. In none were abnormalities of the epicardium, the endocardium or the valves noted.

INTRACRANIAL HEMORRHAGE

In at least 91 cases unexpected death resulted from nontraumatic intracranial hemorrhage. It was estimated that these 91 comprised approximately a third of all cases of spontaneous intracranial hemorrhage that were reported to the institute between 1941 and 1945.

Subarachnoid Hemorrhage from Congenital, Berry or Miliary Aneurysms.

In 48 instances of unexpected death it was proved and in 21 instances it was inferred that death had resulted from the rupture of a thin-walled saccular aneurysm of the type described by Forbus,[4] Bremer [5] and others as congenital, berry or miliary. In the 21 instances in which the subarachnoid hemorrhage was presumed but not proved to have originated from a berry aneurysm, a careful examination of the brain and its vessels had failed to disclose the nature of the vascular defect. It must have been small, and in view of the fact that there was (*a*) no history or evidence of antecedent trauma, (*b*) no systemic disease and (*c*) no other type of abnormality of the brain or the meninges, rupture of a miliary aneurysm was regarded as the probable cause of death. In several of these, one or more intact congenital aneurysms of the circle of Willis were found, but the precise site of rupture was not identified.

A representative case of rapidly fatal subarachnoid hemorrhage which was presumed to have resulted from the rupture of a berry aneurysm is as follows:

> A 29 year old soldier in apparent good health collapsed while running base during a ball game. He got up with difficulty and staggered to the base, where he collapsed, gasped a few times and died. Close questioning of associates failed to disclose any previous complaints or abnormal actions. He was never known to have reported for sick call. There was no history of syphilis, other disease or injury.
>
> When the cranium was opened, an extensive subarachnoid hemorrhage was observed, and there was a small amount of firm clot in the right side of the sylvian fissure, in the vicinity of the middle cerebral artery. No vascular defect was found, and there was no other evidence of cerebral vascular disease.

Age.—The ages of the soldiers in this series whose deaths were known or inferred to have resulted from rupture of a superficial congenital aneurysm are given in table 6. If the 65 cases comprising this

4. Forbus, W. D.: Bull. Johns Hopkins Hosp. **47**:239, 1930.
5. Bremer, J. L.: Arch. Path. **35**:819, 1943.

group constitute a representative sample of cases of sudden death from rupture of a superficial congenital aneurysm it appears that the frequency of sudden death in such cases tends to increase with age between 19 and 39.

Race.—Of 69 soldiers who died of subarachnoid hemorrhage due to rupture of a berry aneurysm, 66 were white and 3 were Negroes.

Obesity.—The relation of body weight to death from rupture of a berry aneurysm was as given in table 7. Although a slightly higher

TABLE 6.—*Age Distribution in Cases of Sudden Death from Rupture of Superficial Congenital Aneurysms (65 Cases)*

Age, Years	Unexpected Deaths from Ruptured Aneurysms, per Cent	Total Army Personnel, per Cent
Under 19	5	9
20-24	14	38
25-29	44	30
30-34	21	16
35-39	15	6

TABLE 7.—*Weight Distribution in Cases of Sudden Death from Rupture of Berry Aneurysms (53 Cases)*

Weight	Sudden Deaths Due to Rupture of Berry Aneurysms, per Cent	Accidental Deaths, per Cent
Very light	1	3.5
Underweight	2	10.5
Normal	28	23.0
Overweight	49	42.6
Very heavy	20	20.4

TABLE 8.—*Relation of Physical Activity to Rupture of Congenital, Berry or Miliary Aneurysms (54 Cases)*

Type of Activity	Estimated Time Spent in Inactivity or Activity, per Cent	Fatal Seizures Coincident with Inactivity or Activity, per Cent
Sleep	33	17
Inactivity—subject awake	17	29
Ordinary activity	33	29
Strenuous exertion	17	24

incidence of sudden death due to ruptured aneurysm is suggested in the "normal" and "overweight" categories than in the corresponding accidental death groups, the number of cases is too few for this to be of statistical significance.

Physical Exertion.—Although the series was scarcely large enough to justify conclusions regarding the relationship of physical exercise to the onset of the fatal seizure, the findings may be summarized as in table 8. It is apparent that there was no statistical evidence to

indicate that physical exertion predisposed to rupture of congenital aneurysms. However, when account is taken of the extreme fragility of these lesions, it seems obvious that a sudden sharp rise in blood pressure might well precipitate rupture. Although there was no instance in which an aneurysm was thought to have been caused or ruptured by direct cranial trauma, the onset of fatal hemorrhage in 9 instances was observed to have been coincident with such exercise as base running in a ball game, wrestling, tennis, drilling, pushing a piano, changing a flat tire, golf, badminton and swimming. The inference that such activities are probably dangerous for a person having a congenital defect in a cerebral vessel is inescapable.

Survival Time After Onset of Fatal Hemorrhage.—In 44 cases of superficial cerebral aneurysm in which the onset of the fatal seizure was witnessed, the average interval between loss of consciousness and death was six hours. It should be borne in mind that the series was arbitrarily limited to cases in which the death occurred within twenty-four hours after the time that the fatal hemorrhage either was recognized or caused loss of consciousness. When the hemorrhage was of the burrowing type, the average survival time was between nine and ten hours, whereas the average survival time when hemorrhage was exclusively extracerebral was less than four hours. Approximately one third of the persons whose hemorrhage was not of the burrowing type died within an hour after loss of consciousness, whereas only 1 whose hemorrhage was in part parenchymatous and in part subarachnoid died during the first hour.

Another matter of interest in relation to time of survival after the onset of the terminal hemorrhage was the presence or the absence of blood in the lateral ventricles. There were at least 30 instances of primary subarachnoid hemorrhage in which the only way that blood could have regained access to the lateral ventricles was by following the normal anatomic route through the fourth ventricle, the aqueduct and the third ventricle. In 21 of these the postmortem examination disclosed blood throughout the ventricular system, whereas in 9 it was specifically stated that the ventricles did not contain blood. When death occurred rapidly (within two hours) after the onset of the fatal hemorrhage, blood was found to have reached the lateral ventricles of some patients and not those of others. Blood was found in the lateral ventricles of all who had survived more than two hours after the onset of the subarachnoid hemorrhage.

Character of Fatal Seizure.—In the majority of cases in which the fatal seizure was witnessed, loss of consciousness was immediately preceded by headache and vomiting and was followed by fecal and urinary incontinence.

Among 69 cases of unexpected death from rupture of a congenital aneurysm there were only 3 in which clinical proof of leakage of blood had appeared before the fatal rupture. In these 3, lumbar puncture disclosed blood in the spinal fluid twelve days, two months and six months respectively before the occurrence of the fatal hemorrhage. It might be argued that the deaths in these cases should not be regarded as unexpected. At the time of the fatal seizure, however, the soldiers not only were ambulatory but were thought to be in good health.

In addition to these 3 there were 16 other cases in which there was anamnestic evidence of cerebral disturbance in advance of the fatal rupture. The most common symptom was headache, which varied in severity, duration and periodicity in the various cases. In some the first headache of which there was record occurred only a few days before death, whereas in others headache had been complained of for many weeks or months. Other anamnestic evidence of intracranial disease included attacks of nausea and vomiting, syncope, convulsions, stiff neck, malaise, emotional disturbances and evanescent nerve palsies. The last-mentioned symptoms were reported in 4 instances, and in all 4 the autopsy disclosed an adherent aneurysm with burrowing hemorrhage.

In 54 cases, either there were no previous signs or symptoms of intracranial disease or the circumstances were such that no anamnestic information was available.

Attention has already been called to the fact that hemorrhage from some of these superficial aneurysms infiltrated and destroyed the adjacent brain tissue whereas the bleeding from others was entirely external. It may or may not be significant that previous or prolonged symptoms of intracranial hemorrhage were present in almost a third of the patients who had burrowing hemorrhages and in only a negligible number of those in whom the hemorrhage was exclusively extracerebral.

It appears that when blood is extravasated into the adjacent brain substance through rupture of a superficial aneurysm the first hemorrhage is less likely to be fatal than when the blood escapes directly into the subarachnoid space. This observation lends support to the hypothesis that a burrowing hemorrhage is the result of some organic fixation of the aneurysm to the adjacent cerebral surface.

Pathologic Observations.—The arterial distribution of the 48 recognized ruptured aneurysms is shown in table 9.

In 6 instances the lesions were multiple, there being one ruptured and one or more unruptured aneurysms of the circle of Willis in the same person. The anatomic distribution of the aneurysms observed in this series was similar to that reported by other authors (McDonald and Korb,[6] Martland[7] and Forbus[4]). Although a frequent site of

6. McDonald, C. A., and Korb, M.: Arch. Neurol. & Psychiat. **42**:298, 1939.
7. Martland, H. S.: Am. J. Surg. **43**:10, 1939.

aneurysm formation was at a vascular junction or bifurcation, such a relationship was not always recorded. In several instances the information available was so scanty that the precise location of the aneurysm on a given vessel could not be determined. Considerably more than half of the aneurysms were found on or anterior to the middle cerebral arteries.

The size of the ruptured aneurysms ranged from 0.3 to 3.0 cm. in diameter, and the defects responsible for fatal hemorrhage varied from what was described as a pinpoint hole to a ragged blow-out of the entire dome of the sac. All aneurysms were described as thin-walled, and in cases in which microscopic examinations were recorded mention was made of the absence of elastic fibers and media. Some were partially occluded by thrombi, but the majority were empty and smooth lined.

TABLE 9.—*Anatomic Distribution of Forty-Eight Ruptured Aneurysms*

	Aneurysms
Anterior cerebral artery and its branches	5
Junction of anterior cerebral and anterior communicating arteries	8
Junction of anterior cerebral and middle cerebral arteries	3
Middle cerebral artery and its branches	15
Junction of internal carotid artery and circle of Willis	2
Junction of middle cerebral and posterior communicating arteries	0
Posterior communicating artery	1
Junction of posterior communicating and posterior cerebral arteries	2
Posterior cerebral artery	3
Junction of posterior cerebral and basilar arteries	3
Cerebellar artery	1
Basilar artery	2
Junction of basilar and vertebral arteries	1
Vertebral artery	2
Total	48

Although several ruptured aneurysms were described as partially surrounded by organized blood clot and some were associated with hematogenous pigmentation of the surrounding meninges, there was poor correlation between clinical and pathologic evidence of bleeding prior to the time of the fatal rupture. This lack of correlation is presumed to be caused by incomplete clinical information in the protocols rather than to freedom from symptoms on the part of those suffering the bleeding.

It was apparent that two types of intracranial hemorrhage resulted from the rupture of superficial aneurysms. In one the hemorrhage was entirely external, with no blood being extravasated into the substance of the brain. In the other there was bleeding into the adjacent brain tissue as well as into the subarachnoid space. There were 46 instances of the former and 22 of the latter.

In the cases in which there was parenchymatous as well as subarachnoid hemorrhage, there was great variation in the extent to which brain tissue had been destroyed. In some the hemorrhage was con-

fined to a relatively narrow zone of the adjacent cortex, whereas in others there was deep extravasation, sometimes communicating with the nearest ventricle. In all but 1 case the hemorrhage involved a cerebral hemisphere. In that instance there was superficial destruction of one lobe of the cerebellum following rupture of an aneurysm of a vertebral artery.

A typical instance of burrowing aneurysm is as follows:

A 34 year old white medical officer experienced sudden severe pain over the right eye, followed by headache, nausea, vomiting and sweating, while walking to the post exchange. He was found to have a facial weakness on the left side, with widely dilated pupils. The fundi were normal. There was diminished auditory air conduction on the left. There was no stiffness of the neck, and the Babinski reflex was normal. The blood pressure was 128 systolic and 60 diastolic. One hour later he appeared confused but claimed that he was free of pain and felt fine. Six and a half hours after the onset of symptoms he was awakened by the return of severe pain over the right eye; he immediately became unconscious, had convulsive movements, was incontinent and three hours later became cyanotic and died.

Inquiry into the previous history revealed that five and one-half months earlier he suddenly had an agonizing pain in his neck, followed by headache and projectile vomiting. He was hospitalized, and a lumbar puncture at that time disclosed numerous red blood cells in the spinal fluid. During his hospital stay of fifteen days a slight paralysis became evident on the lower part of the left side of the face. The headache disappeared, and the patient was discharged to duty, with a diagnosis of subarachnoid hemorrhage of undetermined cause. Six weeks before death he had an evanescent attack of numbness of the left side of the tongue and drooping of the left facial muscles. For twenty-four hours following this attacak he had a mild headache.

The autopsy disclosed subarachnoid hemorrhage originating from a small saccular aneurysm, 8 mm. in diameter, located at the junction of the right middle cerebral artery and a branch that extended toward the island of Reil. The aneurysm had ruptured into the inferior surface of the tip of the temporal lobe, and the parenchymatous hematoma communicated with the inferior horn of the lateral ventricle.

Although studies of the pathologic anatomy did not yield the reason why rupture of some aneurysms resulted in parenchymatous hemorrhage whereas rupture of others did not, they did suggest one explanation sufficiently plausible to warrant consideration. This is that the pressure of an enlarging aneurysm on the surface of the brain or the slow escape and organization of blood in the space between the aneurysm and the brain is undoubtedly capable of eliciting sufficient reactive inflammation to establish adhesions. If the rupture of such an adherent aneurysm occurs through the portion of the wall that is adherent to the brain, it is reasonable to suppose that the blood escapes first into the brain substance and later breaks through the adhesions into the subarachnoid space. The frequent finding of a ragged blood-filled cavity between the super-

ficial aneurysm and the nearest ventricle suggests that this explanation may be valid.

Subarachnoid Hemorrhage from Other Vascular Lesions.

In 4 cases of primary subarachnoid hemorrhage bleeding resulted from some type of vascular lesion other than congenital, berry or miliary aneurysm.

Cirsoid Aneurysm.—A 32 year old white soldier was observed to be "thrashing around" on his bed at 8 p. m. and died forty minutes later. Friends stated that he had been "feeling badly" all day and had complained of headache and malaise.

At autopsy there was evidence of extensive subarachnoid hemorrhage, with bleeding into the left lobe of the cerebellum. The fourth ventricle was full of blood. The source of the hemorrhage was a lesion of the left anterior-inferior cerebellar artery, at first thought to be a cavernous hemangioma and later recognized as a cirsoid aneurysm. There was no other evidence of cerebral vascular disease.

Cavernous Hemangioma.—A 32 year old obese white soldier had an unexpected convulsive seizure at 10:25 a. m. and died one and one-half hours later. He had complained of feeling weak at 9 a. m. but, so far as was known, had no previous complaints and had not reported for sick call.

Autopsy disclosed that both orbital plates were eroded by ovoid cavernous hemangiomas which were situated in part in the frontal fossa and in part in the posterior portions of the orbits. The tumors were deep purple and fluctuant, and one or both of them had ruptured, with resulting subarachnoid hemorrhage.

Angioma.—A 22 year old white soldier, while engaged in ordinary activity, fainted and lapsed into deep coma. Pulmonary edema developed, and death followed eleven hours later. An antemortem lumbar puncture revealed blood in the spinal fluid. Associates reported that prior to the time that the soldier lost consciousness he had complained of headache, had vomited and had seemed restless and talkative.

At postmortem examination subarachnoid hemorrhage was found, which was due to the rupture of a "racemose venous-arterial angioma located in the hippocampal fissure."

Fusiform Aneurysm.—A 38 year old soldier, who had been drinking during the evening, complained of feeling "ill," suddenly collapsed and died, without receiving medical attention.

Autopsy disclosed subarachnoid and intraventricular hemorrhage originating from a slitlike defect in the wall of the right internal carotid artery at its junction with the circle of Willis. The intracranial portions of both internal carotid arteries were the seat of fusiform aneurysms, and at the site of rupture medial hypoplasia was found on microscopic examination.

Intracerebral Hemorrhage from Aneurysms and Tumor.

In 18 of the 91 cases of unexpected death due to intracranial hemorrhage the origin of the bleeding was an intracerebral vessel.

In 5 cases the vascular lesion was recognized macroscopically and confirmed microscopically as an aneurysm. In 3 cases the aneurysm was described as saccular. One aneurysm was mycotic, and another was fusiform and had apparently developed at the site of a congenital

medial defect. In all 5 cases the aneurysm occurred on one or another branch of the middle cerebral artery, and in every instance the hemorrhage had ruptured into a lateral ventricle.

Saccular Aneurysm.—A 27 year old white soldier became nauseated and went to a latrine, where he vomited and collapsed. He died two and one-half hours later, without regaining consciousness. Six weeks prior to death he was said to have had an attack of "grip" which was accompanied with severe frontal headache. Three weeks before death there had been a recurrence of headache.

At the postmortem examination massive central hemorrhage was found in the left hemisphere, from a 4 mm. saccular aneurysm situated on a ganglionic branch of the left lenticulostriate artery. Distal to the aneurysm the lumen of the artery was partially occluded by a laminated thrombus. The hemorrhage communicated with the lateral ventricle, and blood was found throughout the subarachnoid space. There was no other evidence of cerebral vascular disease. The heart weighed 430 Gm., but in view of the fact that the body weighed 89 Kg. and measured 190 cm. in length the heart weight was not considered abnormal. Otherwise the postmortem findings were essentially normal.

A 29 year old white soldier was found unconscious, with evidence of recent vomiting. There were involuntary movements of the arms and the legs. Blood pressure was first 40 systolic and 0 diastolic and was later observed to be 200 systolic and 70 diastolic. The patient did not regain consciousness; acute congestive heart failure developed, and death followed two and one-half hours later.

Postmortem examination revealed massive hemorrhage in the central portion of the right hemisphere, with rupture into the lateral ventricle. On a striate branch of the right middle cerebral artery there was a small saccular aneurysm, which had ruptured. Otherwise the postmortem findings were essentially normal. The heart weighed 314 Gm.

A 19 year old white soldier was found unconscious and died two hours later. There was massive central bleeding into the left hemisphere, and a ruptured small saccular aneurysm was found on the lenticulostriate branch of the left middle cerebral artery. Blood had escaped into the left lateral ventricle. The heart weighed 280 Gm. The postmortem examination failed to disclose any other significant abnormality.

Fusiform Aneurysm.—A 27 year old white soldier had a sudden syncopal attack accompanied by convulsions and died four and one-half hours later, without regaining consciousness.

Postmortem examination disclosed massive intraventricular hemorrhage originating from a fusiform aneurysm of a branch of the left middle cerebral artery. The wall of the aneurysm was described as "firm, yellow, and appears atherosclerotic." Although no weight was recorded, the heart was described as hypertrophic, with "minimal scarring of the musculature and some atheromatous plaques in the coronary arteries and aorta." No other significant abnormalities were noted.

Mycotic Aneurysm.—A 29 year old white soldier was sick in quarters with a "cold" and a furuncle of the anus. He was thought to be doing well until early one morning when he was found in bed in a state of coma. He died two hours later.

About a year previously he had been hospitalized with a diagnosis of "meningitis, mild; type and cause undetermined." At that time he had suffered from severe frontal headaches and stiff neck. A lumbar puncture disclosed bloody spinal fluid.

At postmortem examination there was extensive hemorrhage in the left hemisphere, communicating with the ventricular system. Several thrombotic vessels, the thrombi of which were estimated to be three to four weeks old, were found within the right internal capsule. In the right hemisphere, in the region of the claustrum, a thrombotic aneurysm of the right middle cerebral artery was surrounded by an extensive area of softening.

The terminal cerebral hemorrhage was assumed to have resulted from rupture of a mycotic aneurysm, embolic from the mitral valve. Also secondary to the bacterial endocarditis were an acute splenic tumor and a healed infarct of the kidney.

Intracerebral Angioma.—There were 2 instances of unexpected death due to bleeding from an intracerebral angioma.

A 31 year old white soldier had an attack of headache and vomiting ten hours before death. There had been no recent history of disease or disability. A few minutes before death he had a convulsive seizure, with loss of consciousness.

Postmortem examination disclosed massive intraventricular hemorrhage due to a venous angioma in the floor of the anterior horn of the right lateral ventricle. Cholelithiasis was the only other significant abnormality.

A 19 year old Negro soldier collapsed while writing a letter and died two hours later, without regaining consciousness.

The only significant abnormality seen at postmortem examination was massive hemorrhage due to rupture of a venous angioma, with blood escaping into the right lateral ventricle.

Other Tumors.—Two unexpected and rapidly fatal hemorrhages occurred in cystic brain tumors, one proved and the other presumed to be astrocytoma. One was cerebellar, and the other was in the right frontal lobe of the cerebrum. In one patient the onset of the fatal hemorrhage occurred during sleep and in the other during a period of strenuous exertion. One survived a few minutes and the other two hours after loss of consciousness. Neither had premonitory symptoms for more than a few minutes before loss of consciousness.

Intracerebral Bleeding—Cause Not Recognized.

There were 13 instances of unexpected death due to central cerebral apoplexy in which neither the exact site nor the nature of the vascular defect was recognized. In all of them the hemorrhage was initiated and located in the lenticulostriate region. In 2 cardiac hypertrophy and diffuse vascular disease indicated chronic arterial hypertension. In 2 others there was chronic renal disease without cardiac hypertrophy or diffuse vascular disease. In 8 the hemorrhage had broken through into the lateral ventricle. The ages in this group varied between 20 and 30 years. The only unusual features presented by the patients was their age and their apparent freedom from prodromal symptoms of impending trouble. Most of them died within a few minutes after the onset of incapacitating symptoms. In some the fatal signs occurred during rest or ordinary activity, whereas others collapsed during or

after a period of strenuous physical exertion. The case described in the following abstract is representative of the group.

A 25 year old white corporal collapsed in the dental clinic and died four hours later. There was no other medical history.

Autopsy disclosed a large hemorrhage in the left lenticulostriate region, which had extended into the lateral ventricle. There were secondary hemorrhages in the pons and the medulla. Neither on gross nor on microscopic examination was there any other evidence of cerebral vascular disease. A complete postmortem examination failed to disclose any other significant gross or microscopic abnormality.

MENINGOCOCCEMIA

In 110 of the more than 350 cases of fatal meningococcic infections reported to the Army Institute of Pathology, death occurred within twenty-four hours after the onset of incapacitating symptoms. In 95 of these 110 cases the records were sufficiently complete for analysis.

In 80 of the 95 cases meningococci were recognized by culture or smear of either blood or cerebrospinal fluid. In the remaining 15 the

TABLE 10.—*Age Distribution in Cases of Death from Meningococcic Infections*

Age	All Meningococcic Deaths, per Cent	Sudden Meningococcic Deaths, per Cent	Total Army Personnel, per Cent
18-19	22.7	28.4	9.3
19-24	43.3	47.5	38.1
25-29	19.3	12.5	30.1
30-34	7.8	7.4	16.4
35-39	6.9	4.2	6.1

clinical and pathologic findings were regarded as sufficiently characteristic to justify the diagnosis of meningococcemia despite the absence of bacteriologic proof.

Age.—The age distribution of the sudden deaths from this cause in relation to that of all meningococcic infections and to that of the Army as a whole is given in table 10.

It may be seen that whereas 47 per cent of the Army was comprised of men under 25 years of age 66 per cent of all men who died of meningococcic infections and 76 per cent of those who died suddenly from this cause were under 25. The incidence of rapidly fatal meningococcemia appears to be considerably higher in younger than in older soldiers.

Race.—Fatal meningococcic infection was distributed among white and Negro soldiers as in table 11. It appears from the figures given in table 11 that the incidence of rapidly fatal death from meningococcic infections is greater in Negro than in white soldiers.

Weight and Height.—In table 12 the body weight (corrected for height) of 69 men dying suddenly from meningococcic infection is

compared with the weight of a control group of 296 soldiers who died of accidental mechanical violence. It is apparent that there is no significant difference in weight between these groups.

TABLE 11.—*Racial Distribution in Cases of Death from Meningococcic Infections*

Race	Meningococcic Deaths				Total Army Personnel, Per Cent
	Total		Sudden		
	Number	Per Cent	Number	Per Cent	
White	296	84	74	78	90
Negro	49	14	19	20	10
Others	2	1—	2	2	1—
Unknown	5	1+	..	..	..
Totals	352	100	95	100	100

Prodromal or Prefulminant Phase of the Disease.—In 68 of the 95 cases it was recorded that the patient had been "below par" for varying periods prior to the onset of manifestations of incapacitating illness. The prodromal phase was usually characterized as a mild

TABLE 12.—*Weight Distribution in Cases of Sudden Death from Meningococcic Infections*

Weight	Accidental Deaths, per Cent	Sudden Meningococcic Deaths, per Cent
Very light	3.5	2.9
Underweight	10.5	16
Normal	23.0	17.4
Overweight	42.6	41
Very heavy	20.4	23

infection of the upper respiratory tract or a period of malaise. In 17 instances information regarding prodromal symptoms either was not available or had not been recorded. In none were the prodromal symptoms of sufficient severity to warn of impending catastrophe.

TABLE 13.—*Duration of Prodromal Symptoms in Cases of Death from Meningococcic Infections*

Duration	Number of Cases
Less than 1 hour	6
1-6 hours	9
7-12 hours	15
13-24 hours	12
1-7 days	28
More than 1 week	4

The duration of the prodromal disturbance in the instances in which a history was available was as shown in table 13.

Fulminant Phase.—In most of the 95 cases in which death took place less than twenty-four hours after the onset of incapacitating illness, the transition from the prodromal to the fulminant phase of the infection

was abrupt and overwhelming. Seven of the men died before coming under medical observation, and 6 lived less than one hour after reaching the hospital. Sixty died within six hours after admission to a medical installation.

Because of the shocklike state of collapse associated with fever, cyanosis, cutaneous hemorrhages, rapid pulse, low blood pressure and early development of pulmonary edema, a large proportion of the cases were believed to be examples of Waterhouse-Friderichsen syndrome.[8] In more than half of the group, Kernig's sign or painful or stiff neck was recognized at some time before death. In the majority of these, examination of cerebrospinal fluid disclosed meningococci, inflammatory exudate or both. Despite the frequency (about 50 per cent) with which signs and symptoms of meningocerebral involvement occurred, they were usually masked by those of peripheral circulatory failure. In a few instances manifestations of meningocerebral involvement were predominant throughout most of the brief illness.

Cutaneous hemorrhages were recognized clinically in 54 per cent of the group. The fact that a postmortem diagnosis of cutaneous hemorrhages appeared in 83 per cent of the autopsy protocols is consistent with the extremely rapid progression of the disease process.

In all instances in which body temperature was measured there was fever, and in more than half a reading of 40 C. (103 F.) or higher was obtained at some time before death.

Subnormal systolic and diastolic pressures were observed in almost every instance in which blood pressure was measured.

Pathologic Observations.—In reviewing this group of sudden deaths, we found that 81 of the original 95 cases had sufficiently complete protocols and histologic material for a survey of pathologic changes. The four most frequently recurring pathologic diagnoses were cutaneous hemorrhage, adrenal hemorrhage, leptomeningitis and myocarditis. The frequency of these changes and of the combinations in which they occurred is shown in table 14.

Skin: In 67 of 81 cases cutaneous hemorrhages were observed at autopsy. These varied in severity from a few scattered petechiae to large confluent purple patches over most of the body surface. In some the trunk was more extensively involved than the extremities, and in others the reverse was true. Frequently the distribution was described as "from head to toe." In many instances hemorrhagic lesions were also seen in the conjunctiva and in the buccal mucosa.

The microscopic appearance of the cutaneous lesions varied from simple interstitial extravasations of erythrocytes to hemorrhagic foci of

8. Waterhouse, R.: Lancet **1**:576, 1911. Friderichsen, C.: Jahrb. f. Kinderh. **87**:109, 1918.

TABLE 14.—*Relation of Adrenal Changes to Meningitis, Myocarditis and Cutaneous Hemorrhage*

Categories of Adrenal Change	Cases	Percentage of Total Cases of Adrenal Change	Meningeal Inflammation			Myocardial Exudation			Cutaneous Petechiae or Purpura		
			Cases in Category	Percentage of Cases in Category Showing Meningeal Inflammation	Percentage of All Cases of Meningeal Inflammation	Cases in Category	Percentage of Cases in Category Showing Myocardial Exudation	Percentage of All Cases of Myocardial Exudation	Cases in Category	Percentage of Cases in Category Showing Petechiae or Purpura	Percentage of All Cases of Cutaneous Petechiae or Purpura
Massive adrenal hemorrhage with complete cortical disorganization	45	55	9	20	25	19	42	51	43	96	64
Severe cortical degeneration and focal necrosis with extreme hyperemia and foci of hemorrhage	13	16	7	54	19	8	62	22	11	85	16
Extreme hyperemia and foci of hemorrhage	4	5	2	50	6	3	75	8	4	100	6
Minimal to advanced cortical degeneration and focal necrosis without hemorrhage or severe congestion	14	17	14	100	39	4	29	11	5	36	8
No significant abnormality	5	6	4	80	11	3	60	8	4	80	6
Total	81	100	36	44	100	37	46	[illegible]	67	83	100

acute exudative inflammation. Although bacteriologic studies of the cutaneous lesions were not made routinely, the impression was gained that meningococci were usually found in instances in which smears, cultures or appropriate stains of the cutaneous lesions were made.

Adrenal Glands: Because of the importance that various reviewers have attached to the adrenal changes in persons dying from fulminating meningococcemia and the difficulty that was encountered in attempting to evaluate from the autopsy protocols the degree and the kind of adrenal involvement present, it was decided to reexamine all slides of adrenal glands.[9]

There were 81 cases in which at least one section stained with hematoxylin and eosin was immediately available. Although it was realized that impressions derived from the examination of one or two slides were not necessarily valid for the total adrenal involvement, the results appeared to be of sufficient interest to warrant presentation.

The cases appeared to fall into five principal categories so far as the adrenal involvement was concerned:

1. No adrenal change: In only 5 instances were the adrenal glands regarded as being essentially normal and without evidence of acute degenerative change, excessive hyperemia or hemorrhage.
2. Cortical parenchymatous degeneration with little or no hyperemia or hemorrhage: In 14 instances the adrenal glands, without significant capillary engorgement or hemorrhage, showed retrogressive changes in the cortical parenchyma of the kind characterized by Rich[10] as "tubular degeneration."
3. Hyperemia without significant parenchymatous degeneration: In 4 instances, there was severe hyperemia, most pronounced in the reticular zone and diminishing in severity as the capsule was approached. In some of these, there were focal extravasations of erythrocytes. In 58 instances the adrenal glands were grossly hemorrhagic.
4. Focal hemorrhages with degeneration: In 13 instances, the hemorrhages were focal, and surviving islands of cortex were the seat of striking tubular degeneration.
5. Massive hemorrhagic necrosis: In 45 instances of massive hemorrhage the accompanying cortical disorganization was so great that degenerative cellular changes were largely masked.

Although the involvement was usually bilaterally symmetric, there were some instances in which the hemorrhage was massive in one adrenal gland and focal in the other.

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9. The complete presentation of the histologic changes seen in the adrenal glands in meningococcemia is beyond the scope of this paper, and will appear in a subsequent publication by one of us (N. Z.).

10. Rich, A. R.: Bull. Johns Hopkins Hosp. **74**:1, 1944.

Although the precise sequence of changes that resulted in massive hemorrhagic necrosis of the adrenal glands could not be reconstructed from this study, certain inferences appeared to be justified. The impression was gained that the earliest change was a central hydropic degeneration within the cell masses of the glomerular and fascicular zones of the cortex. In this stage the newly formed central spaces contained only albuminous or fibrillar acidophilic material; later they contained polymorphonuclear leukocytes and debris of necrotic cells. This is the lesion characterized by Rich as tubular degeneration. In some instances the "tubules" may be distended with extravasated erythrocytes. The fact that this form of tubular degeneration without excessive hyperemia or hemorrhage was more commonly found than hemorrhage or excessive hyperemia without degeneration suggested that the parenchymatous lesion was probably primary. Although parenchymatous degeneration started in the glomerular zone and progressed inward, hyperemia characteristically started in the reticular zone and progressed outward. With increasing capillary engorgement, blood tended to escape into the central spaces of the injured cell columns. As the severity of the hemorrhage progressed, disorganization of the cortex occurred, and in its final stages only the reticulum and occasional epithelial cells served to locate the original position of the cortex in the massive perimedullary hematoma. In many instances adrenal glands that were the seat of massive hemorrhagic cortical necrosis were only slightly enlarged. In others they attained weights as great as 100 Gm.

Characteristically, the medulla was spared both hemorrhagic and degenerative change in all but the cases of most severe involvement. Significant antemortem thromboses were suggested in only a few instances.

Meningitis: In 36 of these 81 cases, acute leptomeningitis or meningoencephalitis was recognized. In the majority of these the reactive changes were relatively slight and were microscopic rather than macroscopic. In the instances in which the meningeal reaction was advanced, the changes were typical of acute meningococcic meningitis. It is noteworthy that severe meningeal involvement was rarely seen in association with massive hemorrhagic adrenal necrosis. A plausible inference is that a systemic infection of such severity as to produce bilateral hemorrhagic necrosis of the adrenal glands is likely to result in death before sufficient time has elapsed for the development of a full-blown meningeal reaction.

Myocarditis: No effort was made to appraise the severity or the functional significance of the myocardial involvement. It was apparent from the records that the diagnosis of myocarditis usually referred to an exudation of polymorphonuclear leukocytes overlying a monocytic reaction which was in some instances focal and in other instances diffuse and in some instances sparse and in others dense.

Other Pathologic Changes: In addition, severe pulmonary edema and hyperemia were frequently observed. Petechiae were commonly found beneath the pleura, the epicardium and the endocardium. Acute splenic hyperplasia and cloudy swelling of the liver and the kidneys were noted. Focal hepatitis was recorded in several instances.

Relation of Adrenal Changes to Waterhouse-Friderichsen Syndrome.—The foregoing paragraphs have called attention to the fact that in 58, or 72 per cent, of these sudden deaths from meningococcemia postmortem examination disclosed hemorrhagic lesions of the adrenal glands associated with acute retrogressive changes in the cortex. In the majority of these in which adequate anamnestic data were available the clinical course resembled that of the Waterhouse-Friderichsen syndrome. A typical example is as follows:

A 21 year old Japanese American was admitted to the hospital cyanotic and sleepy, complaining of nonproductive cough and slightly sore throat of two days' duration. Physical examination showed entirely normal conditions except for an injected nasopharynx and a temperature of 104.2 F. He was cooperative, answered questions clearly and undressed himself. Within five minutes of arrival in the ward he was obviously dying. The respiratory rate was 50, and the pulse was imperceptible. The heart sounds were obscured by rales. A purpuric rash was noted over the trunk and the extremities, and the patient died before any further diagnostic or therapeutic measures could be attempted.

At postmortem examination both adrenal glands were grossly hemorrhagic. The meninges were congested, but no exudate was present. Postmortem cultures of the blood were positive for meningococci.

Many of the soldiers whose course was that of the Waterhouse-Friderichsen syndrome also presented some clinical evidence of meningitis. These symptoms included confusion, coma, hyperexcitability and irrationality; delirium sometimes was so severe as to necessitate intravenous sedation. In the following case signs and symptoms of meningeal involvement were superimposed on the peripheral circulatory collapse of the Waterhouse-Friderichsen syndrome.

An 18 year old white soldier entered the dispensary with a chief complaint of nausea and vomiting of twelve hours' duration. The day before he had a sore throat and fever and remained in quarters. On physical examination, the temperature was 102.8 F., the respiratory rate was 32, the pulse rate was 132 and the blood pressure was obtainable. The patient appeared well oriented but nervous and apprehensive. There were generalized petechiae throughout the skin, and the pharynx was injected. There was moderate rigidity of the neck. The purpura increased rapidly, and within two and one half hours the temperature rose to 105.6 F., the pulse rate to 160 and the respiratory rate to 60. Within another hour he was delirious, and he died of respiratory failure four hours after admission. The white blood cell count was 14,400, with 72 per cent polymorphonuclear leukocytes. The clinical diagnosis was acute fulminating cerebrospinal meningitis.

At autopsy a small area of exudate was recognized on the superior surface of the right parietal lobe of the brain and was confirmed microscopically. There was massive hemorrhagic infiltration of the cortex of each adrenal gland.

There were other instances of extensive adrenal hemorrhage in which clinical evidence of meningeal involvement was predominant. An illustrative case of this kind is as follows:

A 20 year old Negro soldier was admitted to the hospital in coma. A history of headache and vomiting during the preceding night was obtained. On physical examination the patient was comatose and restless. The temperature was 104 F., the heart rate was 150 and blood pressure was 74 systolic and 50 diastolic. The pupils were small, and the eyeballs showed a slow rotary nystagmus. Prononunced rigidity of the neck and Kernig's and Babinski's signs were indicative of meningitis. The spinal fluid, however, was clear, with normal dynamics and without increased pressure. The peripheral white blood cell count was 2,850. Despite intensive therapy with sulfonamide drugs and penicillin, the patient went rapidly downhill. Two and one-half hours after admission the heart rate was 170, and the blood pressure was 50 systolic and 0 diastolic. He died three and one half hours after admission. At autopsy there were conjunctival petechiae. The adrenal glands were grossly hemorrhagic although not enlarged. Microscopically, the hemorrhage spared the medulla and was most intense in the zona reticularis of the cortex. Several cortical adenomas were also spared. The zona glomerulosa showed minor degenerative changes. The meninges showed no evidence of inflammatory change either grossly or microscopically. Cultures of blood and spinal fluid were positive for group 2A meningococci.

This case is of especial interest in that clinically it was considered one of meningitis and yet no laboratory evidence of meningitis was found either before or after death.

In 19 of the 81 cases in which a survey of pathologic changes was made, the adrenal glands presented neither gross nor microscopic evidence of hemorrhage. In 4 of these, microscopic examination disclosed moderately severe cortical changes of the "tubular degenerative" type. It is of interest that in all 4 of these cases the characteristic signs and symptoms of peripheral circulatory collapse were present. The following case is illustrative of this group.

An 18 year old white soldier was admitted to the hospital in a comatose condition. He had been found unconscious in a tourist camp; on physical examination, the temperature was 104 F. and the respiratory rate was 62; the pulse rate and the blood pressure were unobtainable. The patient was moribund, cyanotic and gasping for breath rapidly and stertorously. No petechiae were seen. His pupils reacted only sluggishly to light. There was no nuchal rigidity. Bubbling rales and rhonchi were heard on auscultation over the entire chest. The white blood cell count was 33,600. On lumbar puncture 70 polymorphonuclear leukocytes were noted, and smear and culture of the cerebrospinal fluid revealed meningococci. Intensive fluid replacement and treatment with a sulfonamide compound and penicillin were instituted but produced no significant improvement, although the blood pressure rose within seven hours to 78 systolic and 58 diastolic. Respirations became progressively more rapid and shallow, and the patient died fifteen hours after admission. The diagnosis of Waterhouse-Friderichsen syndrome was made.

At autopsy there was pronounced cyanosis of the entire body. The adrenal glands, as well as all other viscera exhibited gross and microscopic congestion but

no hemorrhage. Severe tubular degeneration of the adrenal cortex was present. There was early meningitis, with mononuclear as well as polymorphonuclear leukocytes in the subarachnoid space.

In 10 of the 19 cases in which the adrenal glands were nonhemorrhagic the degenerative changes in the cortex were characterized as minimal. Central liquefaction of cell masses was confined to the glomerular zone and the outer portion of the fascicular zone. All 10 of the patients clinically and pathologically evidenced meningitis. Clinical manifestations of peripheral circulatory collapse were present in some of them.

In 5 of the cases in which the adrenal glands were nonhemorrhagic, the cortical zones showed no evidence of acute retrogressive change. In 4 of these, postmortem examination disclosed advanced purulent leptomeningitis. An example of this group is as follows:

An 18 year old white soldier was admitted to the hospital in a comatose condition. The temperature was 104.2 F., the pulse rate was 88 and the respiratory rate was 22. On physical examination, stiff neck, Kernig's sign and twitching of lips, fingers, toes and arms were evidence of cerebral irritation, but there were no generalized convulsions. Lumbar puncture revealed cloudy fluid containing 14,400 leukocytes, 92 per cent of which were polymorphonuclear leukocytes. Smear and cultures were positive for meningococci. Sulfadiazine was administered intravenously, but the patient sank more deeply into coma and died two and one-half hours after admission.

At postmortem examination, there were no cutaneous petechiae or purpura, and the adrenal glands were grossly and microscopically normal. There were numerous perivascular hemorrhages extending into the cerebral parenchyma. Profound edema was noted in both cortical and subcortical tissue. In some sections the meninges contained a heavy exudate of polymorphonuclear leukocytes, and there was also a considerable leukocytic infiltration of the superficial layers of the molecular layer of the cerebellum.

Clinically Obscure Deaths Due to Meningococcemia.—In general, the correctness of the clinical evaluation of these cases was proportional to the duration of clinical observation. In the majority the duration and the character of the terminal illness were such as to warrant a presumptive or a positive antemortem diagnosis of meningococcic infection. There were many instances in which the illness was so brief and overwhelming that its true nature was not suspected prior to autopsy. The following cases are examples:

At 6 p. m. a 19 year old white soldier complained to the charge of quarters of headache and of "feeling wobbly." When asked whether he wished to go on sick call, he stated that he would wait until morning. Three hours later he again complained of headache, and at 1 a. m. he was heard groaning. At 5.45 a. m. he was found dead in bed. Postmortem examination revealed massive adrenal hemorrhage without meningitis.

A 20 year old white soldier was admitted to an evacuation hospital without previous known history. He appeared restless and somewhat drowsy and was sent

to the medical ward for diagnosis. Thirty-five minutes later he was found dead. At autopsy, discrete and confluent hemorrhages were found throughout the cutaneous surface. The adrenal glands were enlarged, and both cortex and medulla were entirely obscured by massive hemorrhage. Although edema and congestion of cerebral and meningeal vessels were found, there was no microscopic evidence of meningitis.

Sudden Death and the Waterhouse-Friderichsen Syndrome.—Most published reviews dealing with the subject of sudden death give little or no emphasis to meningococcemia as one of the causes. References to rapidly fatal meningococcic infection occur in reviews by Spilsbury [11] and Simpson.[12] Whenever meningococcemia is discussed as a cause of sudden death, the Waterhouse-Friderichsen syndrome is usually described, and death is attributed to the massive adrenal hemorrhage. Although there are many reported cases of sudden death associated with massive adrenal hemorrhage in children, the syndrome seems to have been remarkably rare in adults. Recent reviews treating of the Waterhouse-Friderichsen syndrome include a total of fewer than 30 cases in which the patient was an adult. For this reason the frequency with which massive adrenal hemorrhage was found in soldiers with rapidly fatal meningococcic infection was not anticipated. In approximately 209 of 352 deaths among soldiers due to meningococcic infection, there was some degree of hemorrhage in the adrenal glands. No such incidence of hemorrhage in these glands appears in reports of examinations of autopsy material from civilian sources.

There are several possible explanations of this apparent discrepancy. One is that in many cases of acute fulminating meningococcic infection death takes place early in the disease. As we have stated, in 110 of 352 cases of fatal infection, death occurred in the first twenty-four hours of illness. Many patients were found dead or died within a few hours after the onset of severe illness. In civilian life most of these would have become coroner's subjects, with the result that little or no reliable information concerning the postmortem observations would have been obtained. That the rarity of the Waterhouse-Friderichsen syndrome among civilian adults is apparent rather than real is indicated in a recent report by Dr. Harrison Martland,[13] medical examiner of Essex County, N. J., who collected 9 cases. His series of autopsies following deaths of adults from massive adrenal hemorrhage is the largest described by a single investigator.

The high incidence of sudden death from this cause among soldiers is further explained by the fact that meningococcemia is an epidemic

11. Spilsbury, B., in Rolleston, H.: The British Encyclopaedia of Medical Practice, London, Butterworth & Co., Ltd., 1937, vol. 3, p. 565.

12. Simpson, C. K.: Lancet **1**:851, 1937.

13. Martland, H. S.: Arch. Path. **37**:147, 1944.

disease which is particularly likely to appear when large groups of people are brought together, as in military mobilization.

MISCELLANEOUS CAUSES OF UNEXPECTED DEATH

Early in this investigation the idea of making a statistically significant study of all causes of sudden death of young soldiers was abandoned. Although many deaths from a wide variety of causes had been coded as "sudden," exploration of various other categories of postmortem diagnoses disclosed that death occurring within twenty-four hours after the patient came under medical observation or after the onset of incapacitating symptoms was not always designated "sudden death." To have collected all sudden deaths from every cause would have required individual examination of almost every one of the more than 40,000 autopsy protocols received from 1942 to 1946.

It was apparent from random sampling that a multiplicity of potentially fatal diseases was responsible for unexpected deaths. In many instances it was difficult to understand how a person could have carried on until so short a time before collapse and yet have had so little evidence of illness that he had neither reported for sick call nor appeared to be ill.

Attention has already been called to the fact that the majority of such deaths resulted from organic heart disease, intracranial hemorrhage, meningococcemia or causes not disclosed by postmortem examination. Other occasional and less frequent causes of sudden death are as follows:

1. Adrenal atrophy
2. Aortic rupture
   - Syphilis
   - Arteriosclerosis
   - Idiopathic medial necrosis
3. Diabetes mellitus
4. Diphtheria
5. Encephalitis
6. Glioma (without hemorrhage)
7. Hepatitis, acute infectious (Acute yellow atrophy)
8. Hernia, intestinal obstruction
9. Meningitis (other than meningococcic)
10. Pancreatitis, acute hemorrhagic
11. Pharyngolaryngitis (obstructive)
12. Pneumonia
    - Bronchopneumonia (streptococcic)
    - Lobar pneumonia
13. Septicemia (other than meningococcemia)
14. Thrombophlebitis (pulmonary embolism)
15. Tuberculosis, pulmonary

Although no effort was made to determine the total number of unexpected deaths from each of these miscellaneous causes, it was apparent that the largest number was due to bronchopneumonia. In this group it was the exception rather than the rule when death was reported to have occurred within a few minutes after the onset of the fatal seizure. Usually there was an interval of a few hours or more between collapse and death. On the other hand, many soldiers with this disease were found dead.

CAUSE OF DEATH NOT DISCLOSED BY AUTOPSY

In addition to the deaths from definitely recognized diseases and a large unclassified group excluded because of inadequate clinical, pathologic or toxicologic data, there were at least 140 carefully investigated

cases in which the postmortem findings were esentially normal. Not only did the protocols of these cases indicate that a complete autopsy had been performed, but in most instances the histologic preparations had been reviewed by two pathologists, one at the referring laboratory and the other at the Army Institute of Pathology. Cases in which the postmortem findings were of questionable significance were not included. Thus a death in which the only postmortem finding of consequence was "moderately severe but nonocclusive coronary arteriosclerosis" was rejected. The death could not be classified as one in which the postmortem findings were normal, nor could it be categorically attributed to coronary disease. On the other hand, 16 cases in which the postmortem examination was noncontributory except for "occasional small intimal plaques in the coronary arteries" were classified as "cause of death not disclosed by autopsy."

TABLE 15.—*Age Distribution in Cases of Sudden Death from Causes Not Disclosed at Autopsy (135 Cases*)*

Age, Years	Unexpected Deaths from Obscure Causes, per Cent	Total Army Personnel, per Cent
Under 19	3	9
20-24	36	38
25-29	31	30
30-34	15	16
35-39	15	6

* In 5 instances the exact age was not given, the soldier being described as young.

Also excluded from this group of deaths from unknown causes were those in which there was a reasonable chance that death might have resulted from the ingestion of some unrecognized poison (including alcohol), from anaphylactic shock or serum sickness following a recent inoculation or injection, from heat stroke, from high altitude anoxia or from trauma.

Age.—The ages of the soldiers comprising this group are shown in table 15.

Between the ages of 20 and 35 the number of deaths in each group is in direct ratio to the total number of soldiers in that age range in the Army. It may be seen, however, that soldiers under 20 appeared to be less and those over 35 more likely to die suddenly of undisclosed causes than were men between 20 and 35 years.

Race.—The ratio of Negroes to white persons was 15: 125, which is in fair agreement with the ratio of Negroes to white persons in the Army.

Obesity.—The relation of body weight to the unexpected death of 100 soldiers from obscure causes is given in table 16.

There does not appear to be any significant relationship between body weight and death from anatomicaly obscure causes.

Exercise.—The records of 127 cases were reasonably explicit as to what the soldier was doing at the time of or immediately preceding the fatal seizure. These observations are summarized in table 17.

TABLE 16.—*Weight Distribution in Cases of Sudden Death from Obscure Causes (100 Cases)*

Weight	Sudden Deaths from Obscure Causes, per Cent	Accidental Deaths, per Cent
Most underweight	1	3.5
Moderately underweight	9	10.5
Normal	24	23.0
Moderately overweight	43	42.6
Most overweight	23	20.4

It does not appear in this series that there was any relationship between physical activity and the onset of the fatal episode. The fact that the collapse occurred incident to or immediately after strenuous physical exertion in 23 per cent of the cases indicates that at least this

TABLE 17.—*Relation of Type of Activity to Sudden Death from Obscure Causes (127 Cases)*

Type of Activity	Estimated Time Spent in Inactivity and Activity, per Cent	Fatal Seizures Coincident with Inactivity or Activity, per Cent
Sleep	33	24
Inactivity—soldier awake	17	23
Ordinary activity	33	31
Strenuous exertion	17	23

number of soldiers probably felt reasonably well until a short time before collapse and death. That the fatal collapse of these apparently healthy persons was not invariably a vasomotor phenomenon activated by some extrinsic stimulus was indicated by the fact that in about

TABLE 18.—*Survival Time After Onset of Fatal Seizure*

Time	Cases
Few minutes or less	93
More than a few minutes and less than 60 minutes	4
Between 1 and 24 hours	4
Not known or not recorded	39

24 per cent of them the fatal seizure occurred during sleep or immediately after waking.

Survival Time After Onset of Fatal Seizure.—The rapidity with which death occurred after the onset of incapacitating symptoms is shown in table 18.

State of Health Immediately Preceding the Fatal Seizure.—The information recorded with regard to the state of health during the twenty-four hours that preceded collapse is given in table 19.

TABLE 19.—*State of Health Preceding Collapse*

State of Health	Cases
"Did not feel well"	10
Substernal or epigastric discomfort	9
Acute psychotic episode with extreme agitation	8
Headache	7
Infection of the upper respiratory tract	3
Vomiting	3
Normal or not stated	100

TABLE 20.—*Characteristics of Fatal Seizure*

Observation	Cases
Simple syncope (rarely preceded by vomiting or followed by labored respiration)	68
Convulsions	17
Substernal or epigastric pain and syncope	9
Headache and syncope	2
Not known or not recorded	44

Nature of the Fatal Seizure.—In 96 instances, the attack was witnessed, and its characteristics were recorded. These are summarized in table 20.

Past History.—In the majority of these cases, either there was no comment regarding the previous health or it was reported as having been good. In 10 instances a history of previous convulsive seizures suggested epilepsy.

TABLE 21.—*Postmortem Findings in 140 Cases of Unexpected Death from Obscure Cause*

Findings	Cases
Agonal changes	
Cardiac dilatation	13
Pulmonary edema and congestion	69
Generalized congestion of viscera	19
Disseminated petechiae	12
Cerebral petechiae	4
Evidence of disease	
Obesity	23
Cardiac hypertrophy (over 400 Gm.)	18
Coronary arteriosclerosis (occasional small atheroma)	16
Focal myocarditis (mild and of doubtful significance)	3
Fat infiltration of right ventricle	2
Craniocerebral adhesions	2
Purulent bronchitis	1
Chronic catarrhal bronchitis (chronic asthma?)	1
Interstitial pneumonitis (mild and of doubtful significance)	1
Generalized arteriolar sclerosis	1
No pathologic change	33

Pathologic Observations.—The postmortem findings in this group are summarized in table 21.

It is apparent that the most frequent postmortem changes noted in this group are classifiable as agonal changes and are probably indicative of acute circulatory failure or acute systemic anoxia. Certainly whatever evidence there was of disease was not adequate to explain the unexpected failure of circulation or of respiration which was the immediate cause of death. The most frequently encountered evidence of disease was cardiac hypertrophy. In only 1 instance, however, did the weight of the heart exceed 450 Gm. In this case the cardiac hypertrophy was accompanied by diffuse vascular disease.

There is little to be said in summary of the pathologic observations other than to reiterate that the methods of examination available to the pathologist (or the toxicologist) are frequently inadequate to disclose either the extent or the nature of disorders even though they are of sufficient severity to be incompatible with life.

SUMMARIZING COMMENT

From an incomplete survey of the autopsy material at the Army Institute of Pathology it was estimated that reports of approximately 1,000 sudden deaths from disease of apparently healthy soldiers between 18 and 40 years were received between 1942 and 1946. Although an attempt to review all of them was not made, an examination of between 700 and 800 indicated five principal categories:

Heart Disease.—There were approximately 350 sudden deaths from previously unrecognized heart disease. Almost 300 of these were due to coronary arteriosclerosis. The following facts and opinions were derived from an analysis of the data on 115 soldiers whose deaths were from coronary disease.

Eight per cent of the group were under 25 years of age, and 22 per cent were younger than 30. White and Negro soldiers were represented in proportion to their numbers in the Army.

Although the body weights of these soldiers as recorded in the autopsy protocols were significantly greater than those recorded for healthy inductees, this was equally true of the weights recorded in the autopsy protocols of soldiers dead of accidental injuries from firearms, traffic accidents and acute infections. It was concluded that the figures for body weights in these autopsy protocols were usually estimates and should be used with reservation to judge the relationship of obesity to any given disease.

The frequency with which the onset of the fatal attack of coronary insufficiency occurred during a period of strenuous physical exertion lends support to the prevalent and plausible opinion that violent exercise is probably dangerous for persons suffering from severe coronary disease. That this information is not of great practical value to the Army in the prevention of such casualties is indicated by the fact that none

of these soldiers was suspected of having heart disease prior to death and that even in retrospect fewer than 25 per cent of them had a history of symptoms that may have been of cardiac origin.

The practicability of conducting complete cardiologic studies on all soldiers who admit having occasional twinges of abdominal or epigastric discomfort or of relegating them to a limited service status is dubious to say the least.

In all instances postmortem examination disclosed severe atherosclerosis of one or both coronary arteries. Thrombotic occlusion was recognized in approximately 25 per cent, and it was apparent that in most of these the fatal thrombus had begun to form some hours or days before it became symptomatic. In an additional 20 per cent the occlusion was attributed to atheromatous change. Bleeding into an atheromatous plaque was an infrequent cause of occlusion. In 55 per cent of the group no site of complete occlusion was found.

Intracranial Hemorrhage.—In 69 of 91 reviewed cases of sudden death from nontraumatic intracranial hemorrhage the bleeding was principally subarachnoid and was either proved or inferred to have resulted from the rupture of a superficial aneurysm of the congenital or berry type.

The frequency of sudden death from this cause tended to increase with age between 18 and 40 years. The incidence was similar in white and Negro soldiers. There was some indication that aneurysms of this type are more likely to rupture during a period of violent physical exertion than during sleep. About 20 per cent of these soldiers gave a history of headaches.

At autopsy the bleeding was found to be confined to the subarachnoid space in about 65 per cent and was both parenchymatous and subarachnoid in 35 per cent. The latter type of hemorrhage was usually due to the rupture of an aneurysm which had become attached to or had burrowed into the adjacent cortex. Although many soldiers died during their first episode of hemorrhage, others showed postmortem evidence of previous bleeding that had not been recognized clinically.

Meningococcemia.—In 110, or approximately one third, of all reported cases of death from meningococcic infections, death occurred within twenty-four hours after the onset of incapacitating symptoms. The incidence of fatal meningococcemia bore an inverse relationship to age and was higher in Negro than it was in white troops.

More than half of the patients in this group died within six hours after coming under medical observation. In approximately 70 per cent of the cases, the soldier was reported to have been below par or to have been suffering from a mild infection of the upper respiratory tract prior to the onset of the fulminating phase of the disease. It was

apparent that no "cold" or minor indisposition complained of by a soldier who may have been exposed to persons with meningococcic infections should be ignored. The majority of those who died after a fulminant phase of twenty-four hours or less had unheeded warning of the impending catastrophe.

Many were found dead or died before there was opportunity for clinical study. In a few instances, the signs and symptoms were predominantly those of meningitis, and circulatory failure was terminal. The majority, however, were characterized clinically as suffering from the Waterhouse-Friderichsen syndrome, some with and many without evidence of meningeal invasion.

At autopsy purpura or cutaneous petechiae were recognized in over 80 per cent of these men. Focal or massive adrenal hemorrhages were encountered in 71 per cent. In most of the hemorrhagic and the nonhemorrhagic adrenal glands, microscopic examination of the cortex disclosed degeneration and necrosis of the "tubular" type.

Although there was no instance in which the Waterhouse-Friderichsen syndrome was reported to have been observed in a person whose adrenal glands were found to be normal, adrenal hemorrhage was not prerequisite to the occurrence of a shocklike state of collapse nor was it invariably associated with bleeding into the skin. Adrenal apoplexy occurred without cutaneous hemorrhage, and cutaneous purpura was encountered without hemorrhage of the adrenal glands.

The impression was gained that adrenal hemorrhage in fulminating meningococcemia was usually preceded by degenerative changes in the cells of the glomerular and fascicular zones of the cortex. Medullary damage was characteristically absent, minimal or terminal. Gross or microscopic evidence of meningitis was present in 44 per cent and of myocarditis in 46 per cent of all cases.

Miscellaneous Causes of Sudden Death.—Although inflammatory, degenerative and neoplastic diseases of wide variety were encountered as occasional causes of sudden death, the number of deaths resulting from any one of them was not of the same order of magnitude as those of the three previous groups. The impression was gained that the total number of reported sudden deaths from miscellaneous causes was probably between 200 and 400 and that infections of the respiratory tract accounted for the largest subgroup.

Obscure Causes.—There were at least 140 carefully investigated sudden deaths in which the postmortem findings were essentially normal. Complete pathologic examination, supplemented in many instances by toxicologic studies, failed to disclose the cause of death. It was estimated that they represented more than 10 per cent of all sudden nontraumatic deaths of apparently healthy young men.

The racial and the age distribution of the soldiers dying of obscure causes corresponded to those of the Army as a whole. Their weights did not differ from those of soldiers dead of accidental violence or of acute infections. The majority either were found dead or died within a few minutes after a syncopal attack.

In 8 instances death was preceded by an acute psychotic disturbance manifested by violent emotional and physical agitation. In 10 instances there was a past history of convulsive seizures suggestive of epilepsy.

There was no apparent relationship between the onset of the fatal seizure and what the soldier was doing at the time of the attack. Thus, the number of seizures that occurred during sleep or during strenuous exertion was roughly proportional to the number of hours that the average soldier devoted to such activities.

There is little to be said in summary of the pathologic observations of this group other than to reiterate that the methods of examination available to the pathologist are frequently inadequate to disclose either the extent or the nature of certain disorders even though they are of sufficient severity to be incompatible with life.

FINAL SUMMARY

Survey of the postmortem material at the Army Institute of Pathology revealed that the most common diseases responsible for rapid, unexpected death among young soldiers were heart disease, intracranial hemorrhage and meningococcemia. Of the many miscellaneous diseases also recorded, pneumonia occurred most frequently. In addition there was a group of deaths for which no cause could be established.

The most common form of heart disease responsible for sudden death was severe coronary arteriosclerosis with or without demonstrable thrombosis. Rupture of an aneurysm of the circle of Willis was the most common cause of rapidly fatal intracranial hemorrhage. Degeneration of and hemorrhage into the adrenal cortex were regarded as important contributing causes of rapid collapse and early death incident to meningococcemia.

CARDIOAORTITIS

Report of a Case

NIELS DUNGAL
REYKJAVIK, ICELAND

INFLAMMATIONS of the aorta are commonly considered to be traceable to one of two causes: syphilis and rheumatic fever. Jores [1] maintained that a productive inflammation of the aorta may practically always be traced to syphilis. In European institutes it has perhaps been taken far too much for granted that all kinds of productive aortitis are of this origin and closer inquiries neglected for that reason.

Klotz [2] described inflammation of the aorta from a nonsyphilitic cause in 1915 and Von Glahn and Pappenheimer [3] described arteritis of rheumatic origin in 1926. In all countries the sporadic occurrence of periarteritis nodosa has fanned the interest in arterial inflammations of nonsyphilitic origin, leading to the important observations of Rich that those lesions are traceable to anaphylactic hypersensitivity.

The case to be described here may fall into this group, although its final cause remains unexplained.

REPORT OF CASE

April 3, 1940 a man 22 years old was received in the medical department of the state hospital in Reykjavik. He came from the country, where he had lived all his life, having but little communication with the outside world. His father had died of heart disease, and his mother had, in her youth, recovered from tuberculosis. The patient was in good health until the age of 12 years, when he began to have pains in various joints with fever, which sometimes rose to 40 C. (104 F.). These attacks recurred again and again but only rarely lasted longer than a few days. In the summer of 1936, exposure to cold was followed by lasting fever, and he lay in a provincial hospital with the diagnosis of his condition uncertain. There was no expectoration during this fever, but the patient had swollen glands on both sides of his neck. Some of these glands were incised, apparently without evacuation of pus, and after a month the wounds were healed.

In May the patient suffered from severe pains in the head and on that account lay in bed for a month at home. He was then thought to have meningitis, but recovered.

In April 1938 the patient's health got worse, and all the time he had enlarged glands in the neck.

From the Department of Pathology, University of Iceland.

1. Jores, L., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie, Berlin, Julius Springer, 1924, vol. 2, p. 667.

2. Klotz: J. M. Research **31**:409, 1915.

3. Von Glahn, W. C., and Pappenheimer, A. W.: Am. J. Path. **2**:235, 1926.

In the winter of 1940 he had an attack of influenza, and his glands enlarged once more. His strength gave away, but he had no pains and no expectoration. When the patient was hospitalized, his right pupil was considerably wider than the left, and he had only 50 per cent vision with the left eye. Under the right mandibular angle were enlarged glands of cherry size, and similar but less enlarged glands were palpable on the left side. There were no enlarged glands in the axillas.

Ophthalmoscopy revealed old adhesions between the iris and lens.

On April 30 the patient had a chill and complained of pains in both ankle joints, while the fever rose to 39 C. (102.2 F.). These attacks were repeated several times until the patient died, May 23. During the last days of life he had convulsions, and the blood urea rose to 200 mg. per hundred cubic centimeters.

Observations made at the hospital were as follows: The blood pressure was 125 systolic and 90 diastolic. The hemoglobin was 73 per cent (Sahli). The erythrocyte sedimentation rate was 125 mm. in one hour. The urine contained albumin and pus but no sugar. By Esbach's reagent the albumin in the urine was 10 per cent. The erythrocyte count was 4,320,000; the leukocyte count was 3,228, of which 22 per cent were segmented and 48 per cent unsegmented neutrophils, with lymphocytes 30 per cent.

Autopsy.—The body was 185 cm. long and not emaciated. There was slight edema around the ankles.

No adhesions were noted in the thoracic or the abdominal cavity.

The heart weighed 520 Gm. and was smooth on the surface. No fibrosis was visible in its musculature, and the endocardium was smooth, Behind the semilunar valves the lining of the aorta was distinctly changed; a finely wrinkled sack was seen behind each valve, yet the sacks did not resemble aneurysms, as the distention was so diffuse that its limits were hardly discernible, but the size of each sack corresponded to that of a grape. The valves themselves were smooth and thin, with no macroscopic changes.

The aorta had no apparent changes in the ascending part, but in the descending part of the thoracic portion changes were seen similar to those at the base, i. e., wrinkled, slightly bulging patches where the intercostal arteries branched from the aorta. These wrinkled patches were about the size of a dime, all soft and uncalcified.

Below the diaphragm these changes were much more conspicuous. A slight dilatation was noticeable where the superior mesenteric artery branched from the aorta, and from there downward the aorta in its entirety was more or less thickened and wrinkled, with light brown patches. When cut, the tissue was soft, white and without any resemblance to lipoid material, and no calcifications were found. The whole wall was soft and appeared to be less elastic than normally.

The lungs showed no abnormality. In both hilar regions enlarged lymphatic glands were seen, especially on the right side, where chalklike caseations were present in some glands, and on the left side one gland was found thoroughly calcified. Caseated glands were found extending along the veins of the neck on both sides.

The liver was greatly enlarged, weighing 2,700 Gm., and was of rather increased consistence. Its surface was smooth and brownish; the cut surface appeared fairly normal.

The spleen weighed 700 Gm. and was of medium consistence and dark red on the cut surface.

Both kidneys were greatly enlarged, each weighing 320 Gm. They were of the same appearance: the surface, light gray; the capsule, easily detached; the parenchyma, light gray, without distinct limits between pyramids and cortex.

Nothing conspicuously abnormal was seen in the intestinal tract.

The tonsils were not enlarged. The thyroid gland weighed 27 Gm.

The brain was unusually heavy, weighing 1,740 Gm., but was without apparent abnormalities. The hypophysis weighed 0.68 Gm., and was apparently normal.

Blood Cultures.—Blood agar and ordinary mediums were inoculated from the blood of the heart. No growth was obtained.

Kahn Test.—The Kahn test was made on the blood while the patient was alive and also after his death, but with negative results.

Histologic Examination.—(*a*) Liver: There was conspicuous hyperemia, and the central venules were considerably dilated. The hepatic cells were fairly well outlined, but the trabecular structure was partly destroyed by the distended capillaries.

(*b*) Aorta: The aortic wall was greatly thickened, chiefly from hyaline fibrous tissue. This increase in thickness was mainly due to thickening of the intima, which was hyaline, but in some places it contained smaller or larger cell infiltrations, consisting mostly of neutrophil leukocytes, endothelioid cells and histiocytes scattered in a necrotic tissue where nuclear destruction was prominent among small and partly larger hemorrhages. Small infiltrates of leukocytes were seen scattered in many places, particularly around vessels, some of which were fairly wide in the media, which in its entirety was greatly thickened by fibrosis. Hyaline necrosis was seen in some places in the connective tissue, and in between these foci smaller and larger fluid-filled spaces were seen, as if colliquative necrosis had taken place. Some of these spaces contained a number of large cells with small nuclei and large amounts of protoplasm, which would be only faintly stained, giving the appearance of water-logged protoplasm. Similar cells could also be seen scattered in the intima. Many clefts were seen in the tissue, some filled with blood, but others not. In the vasa vasorum no intimal changes could be seen, but around some of them were small heaps of lymphocytes. In the connective tissue a scattered infiltration of segmented leukocytes was taking place, if no heaps of them were present. Of the cells surrounding the vasa vasorum, a considerable proportion consisted of plasma cells. No micro-organisms were found.

(*c*) Heart: A quick survey showed little change in the heart, but on closer search scattered small accumulations of segmented leukocytes and plasma cells were found, most of them slight. In one such accumulation, which was among the largest and consisted chiefly of histiocytes, a structureless substance was seen between the cells, which appeared to consist of fibrin. Most of the cells were lymphocytes and monocytes, with a few plasma cells and fewer endothelioid cells. In some places fibrotic patches were noted, with some remnants of muscular tissue still discernible.

(*d*) Kidneys: The glomerular capillaries were for the most part hyalinized, and in some of them no cells could be seen, but only a structureless substance which retained the form of capillary tufts. Staining with gentian violet displayed much amyloid in the malpighian corpuscles and in some places in the convoluted tubules.

COMMENT

The disease described here does not to my knowledge conform with any previously described. The macroscopic and microscopic

changes were different from those seen in rheumatic involvements. And in recurrent rheumatic disease endocardial changes would be expected, which were not present in this case. Aschoff's nodules were not found, and the aortic changes were prominent in the intima and the media, instead of being limited to the adventitia as they usually are in rheumatic infections. The pericardium had never been involved, the pathologic process being limited to the muscular tissue of the heart.

Syphilis can be excluded with certainty. Not only were the blood tests negative, but the aortic changes were most pronounced in the abdominal portion, not in the thoracic part as is the rule in syphilis. Besides this man was far too young for mesaortitis to have had time to develop, and there is no reason to suspect syphilis in a man who had stayed all his life in an out of the way rural community where syphilis is unknown.

We can therefore with great probability exclude a syphilitic as well as a rheumatic infection as the cause of this disease.

The patient had a tuberculous involvement of the lymphatic glands of his neck. This was microscopically found to be a typical caseous tuberculous process which was in no way similar to the changes found in the heart and the aorta.

The patient appears, then, to have been suffering from two diseases at the same time: tuberculous infection of the cervical lymph glands and a different process involving his vascular system, particularly pronounced in the heart and the aorta but manifesting itself also in the amyloid nephrosis of the kidneys. The enlargement of the spleen was partially due to amyloidosis but probably only partially, as it is unusual to see such great enlargement of the organ from amyloidosis alone.

The changes in the liver were noteworthy, as there was excessive hyperemia without any definite signs of venous stasis.

Culture mediums inoculated from heart blood and spleen remained sterile and one is therefore not justified in assuming a streptococcic origin of the infection.

I have not been able to find any report of a corresponding case in the literature. In typhus and scrub typhus, according to Allen and Spitz,[4] similar changes may be observed in the aorta, although in a lesser degree, but a typhic origin can be excluded in this case.

Klotz [2] has published a case of aortitis in which the inflammation was limited to the places in the aortic wall where the intercostal arteries branch out from it. The changes in his case seem to have been similar to those described here.

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4. Allen, C. A., and Spitz, S.: Am. J. Path. **21**:603, 1945.

Chiari [5] and Marchand [6] have suggested that a smaller or greater number of the cases classified as instances of aortitis of syphilitic origin may have nothing to do with syphilis.

Sproul and Hawthorne [7] have described a case of chronic diffuse mesaortitis which had no relation to syphilis. But the patients were old patients. The aorta was macroscopically unchanged, and no symptoms of infection were mentioned in the anamnesis. The aortitis described here is therefore apparently different.

A case similar to mine has been described by Mallory [8]:

> The patient was a 35 year old man. Four years before death he began to suffer from pains in his feet, with signs of inflammation in the metatarsal joints. A year later he was troubled by pains in his chest, and at intervals he had pains in various joints, but never acute arthritis.
>
> Behind the aortic valves and in the initial 2.5 cm. of the ascending aorta was a pannus-like thickening of wrinkled fibrotic pink tissue, but no atheromatosis was visible. All valves were intact, and nowhere was there a sign of rheumatic involvement. The heart was greatly hypertrophied, weighing 900 Gm.
>
> Microscopically, the connective tissue was greatly increased, with slight, if any, inflammatory reaction. Accumulations of lymphocytes were found along the vasa vasorum and considerable perivascular infiltration of the adventitia was noted, forming a striking resemblance to acute syphilis.

The same author mentioned another case:

> A 25 year old man six years before had fallen ill with swellings of the joints of his feet and had suffered from that affliction for two years. Later his carpal joints were affected, and then those of the spinal column, but yet he kept on working. Some time later all his arthritic inflammations flared up, and his condition led to death.
>
> At autopsy the heart was enlarged, weighing 580 Gm., and much the same changes were noted in the aorta as in the case previously described, but the changes reached only 1 cm. into the aorta. On the other hand, the process reached onto the endocardium in the ventricle below the semilunar valves. Microscopically the picture was similar except that the infiltrate of leukocytes, monocytes and lymphocytes was more pronounced. Mallory [8] found these changes greatly resembling acute syphilis. In the heart the muscular tissue was found degenerated with fibrosis.

Mallory said that most pathologists would have classified his cases as instances of syphilis but that, although he was unable to prove that the changes described were not of syphilitic origin, he must have serious

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5. Chiari, H.: Verhandl. d. deutsch. path. Gesellsch. **15**:137, 1904; cited by Jores.[1]

6. Marchand, F.: Verhandl. d. deutsch. path. Gesellsch. **15**:197, 1904; cited by Jores.[1]

7. Sproul, E. E., and Hawthorne, J. J.: Am. J. Path. **13**:311, 1937.

8. Subacute Aortitis and Aortic Endocarditis, Etiology Unknown, Cabot Case 22141, New England J. Med. **214**:690, 1936.

doubts in that respect. He suggested that his cases may be instances of a disease of some unknown origin, perhaps a disease to be considered as precursory to the inexplicable calcifications in the cardiac valves of old people, which as a rule are not accompanied by endocarditis.

Holman [9] in a series of papers has shown that acute arteritis can be produced in dogs if they are fed a low protein diet and at the same time suffer from renal insufficiency.

The excessive amyloid nephrosis in the present case without corresponding amyloidosis of other organs may have been a causative agent in producing the acute aortitis. This amyloid nephrosis in all probability caused hypoproteinemia, although I have no proof of that condition, as serum protein determinations were not made.

Rich and Gregory [10] have shown experimentally that lesions with the basic characteristics of rheumatic carditis can be the result of anaphylactic hypersensitivity.

Rich [11] has demonstrated the causal relationship between allergic hypersensitivity and periarteritis nodosa. Holman [9] mentioned also the apparent connection between renal insufficiency and periarteritis nodosa.

The unusually outspoken vascular changes in my case might be the result of hypersensitization following or concomitant with the renal lesion, although the mechanism remains obscure. Although this patient had a tuberculous infection which could have furnished the allergen, other antigenic agents might have been responsible.

SUMMARY

Severe cardioaortitis occurred in a 22 year old man. Syphilis could be excluded, and the clinical and pathologic picture was not that of a rheumatic infection. It is suggested that allergic hypersensitivity may have been the basic causative factor.

9. Holman, R. L.: Am. J. Path. **19**:147 and 159, 1943.
10. Rich, A. R., and Gregory, J. E.: Bull. Johns Hopkins Hosp. **73**:239, 1943.
11. Rich, A. R.: Bull. Johns Hopkins Hosp. **71**:123 and 375, 1942.

DISTRIBUTION OF ALKALINE PHOSPHATASE IN THE HUMAN LIVER

A Study of Postmortem Material

M. WACHSTEIN, M.D.
MIDDLETOWN, N. Y.
AND
F. G. ZAK, M.D.
NEW YORK

IN PREVIOUS reports we [1] described the morphologic distribution of the alkaline phosphatase of the liver as observed under various experimental conditions. In the present investigation the distribution of the enzyme was studied in tissue sections of the livers of patients who had died with hepatic diseases and the livers of patients who had succumbed to other illnesses.

METHOD

Gomori's [2] method as modified by Kabat and Furth [3] was employed. There were some minor alterations of the technic previously described, as follows: The time during which sections were incubated in the buffer-phosphatase mixture was prolonged to twelve to fourteen hours. If, however, abundant amounts of phosphatase were revealed, the sections were incubated for only two hours. No counterstain was used. Control scetions were treated in an identical manner save for the fact that the glycerophosphate was omitted from the incubation mixture. In most of the cases, material was used only if the autopsy was done within eight hours or less after death. In a few instances a longer period had elapsed between death and autopsy. In control experiments, carried out on animal organs, it was seen that the time factor up to forty-eight hours was negligible.

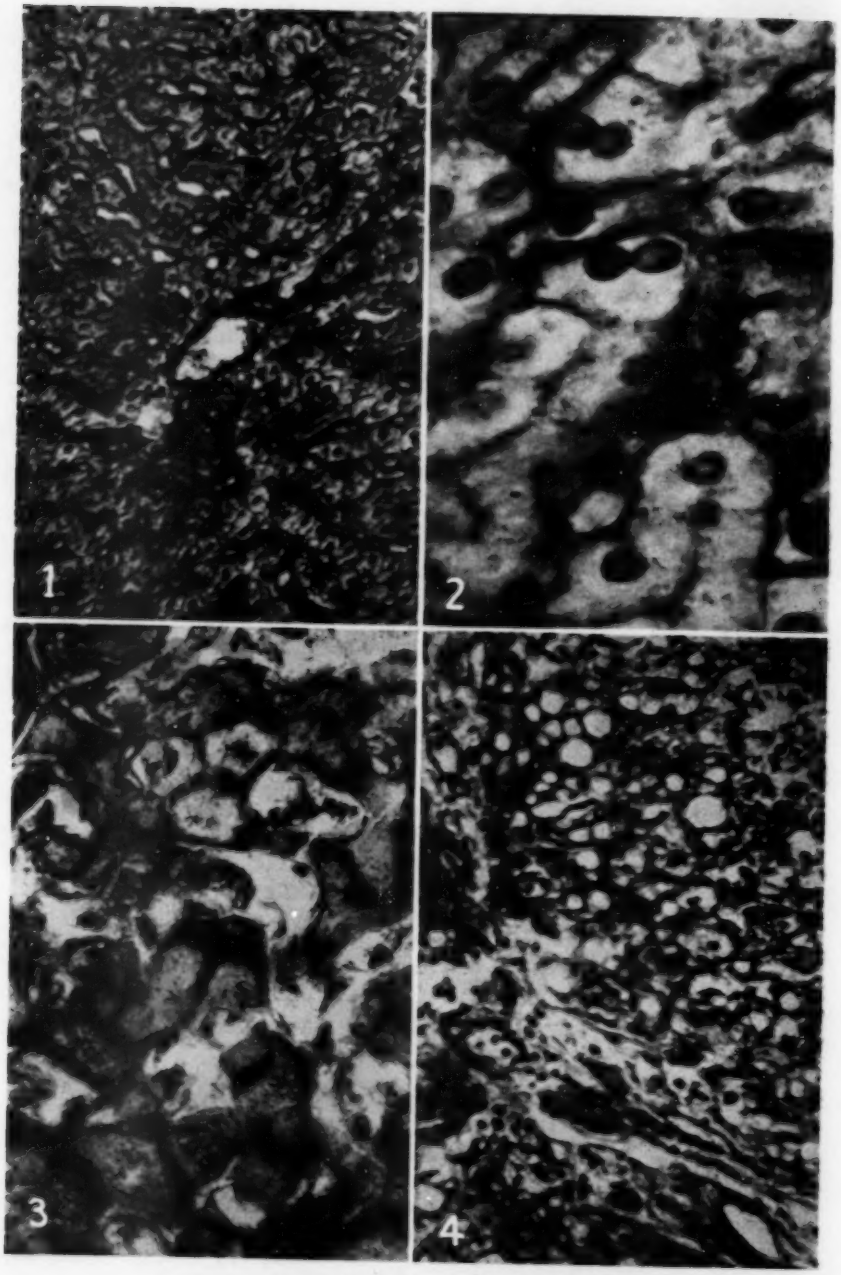
ALKALINE PHOSPHATASE IN THE NORMAL LIVER

The liver of a 22 year old man who died a violent death and on whom the autopsy was done within half an hour was studied, as well as livers from 36 patients ranging in age from 6 months to 72 years. The livers of these patients, who had died from various diseases, were normal grossly and microscopically.

The cytoplasm stained only faintly, with occasional cell groups showing more intense reactions. In general the nuclei contained the enzyme, in the chromatin, the nucleoli and the nuclear membrane.

From the Laboratories of the Division of Pathology, Mount Sinai Hospital, New York, and the Elizabeth A. Horton Memorial Hospital, Middletown, N. Y.

1. (*a*) Wachstein, M.: Arch. Path. **40**:57, 1945. (*b*) Wachstein, M., and Zak, F. G.: Proc. Soc. Exper. Biol. & Med. **62**:73, 1946.
2. Gomori, G.: Proc. Soc. Exper. Biol. & Med. **42**:23, 1939.
3. Kabat, E. A., and Furth, J.: Am. J. Path. **17**:303, 1941.



FIGURES 1 TO 4

(See legends on opposite page)

Occasionally, the entire nucleus took the stain. There was a varying degree of phosphatase activity in the walls of the sinusoids and in the Kupffer cells. In cases with much activity in the sinusoidal walls, there was often uneven staining. Phosphatase was demonstrated in a varying degree in the nuclei of the epithelium of the bile ducts. The endothelium of the larger veins and particularly of the small arteries and arterioles was frequently the site of conspicuous activity. The lymphocytes found in the portal fields showed inconstant amounts of phosphatase. The bile capillaries likewise displayed considerable variation in their staining reaction. In some instances, including the case of violent death, they were well outlined, while in others they were not visible (figs. 1 and 2). They appeared as fine black lines; occasionally there was a distinct lumen. On cross section they were observed as minute black dots. In several livers, apparently normal, an incubation period longer than two hours caused loss of the sharp delineation of the bile capillaries and produced a widening of the stained zone.

Not infrequently fine black granules were scattered in the vicinity of the bile capillaries. It is probable that some of this activity is localized in the Golgi apparatus. Alkaline phosphatase activity was first demonstrated in the Golgi zone of the intestinal epithelium [4] and has also been observed in the liver cells.[5] However, care must be taken in interpreting dark granules in liver cells as signifying phosphatase activity. Hemosiderin granules take a dark color owing to the formation of iron sulfide. Lipofuscin usually can be recognized by the more yellowish tinge, although occasionally it takes a darker color similar to that of ceroid, the pigment of experimental dietary cirrhosis.[1a] In addition, calcium, which may sometimes appear in small granules, will also stain black. It is therefore necessary to check the specificity of the staining reaction by means of control sections incubated in a sub-

4. Emmel, V. M.: Anat. Rec. **91**:39, 1945.

5. Deane, H. W., and Dempsey, E. W.: Anat. Rec. **93**:401, 1945. Dempsey, E. W., and Wislocki, G. B.: Physiol. Rev. **26**:1, 1946.

EXPLANATION OF FIGURES 1 TO 4

Fig. 1.—Alkaline phosphatase activity in the liver of a 22 year old man who died a sudden violent death. The sites of activity stain dark. There is prominent activity of the walls of the sinusoids. The bile capillaries appear as fine black lines. × 125.

Fig. 2.—A similar preparation of the same liver at a higher magnification. × 600.

Fig. 3.—Alkaline phosphatase activity in the liver of a patient with obstructive jaundice. The bile capillaries show conspicuous activity. × 450.

Fig. 4.—Alkaline phosphatase activity in the liver of a child with diffuse acute necrosis of liver cells. The cells in the periportal areas are preserved but show fatty changes, while all other cells are necrotic. The necrotic cells show a normal amount of enzymatic activity. × 125.

strate mixture without glycerophosphate in each single case in which black granules are visualized.

OBSTRUCTIVE JAUNDICE

One biopsy and 9 autopsy specimens were studied. Obstruction of bile ducts occurred as a sequela of carcinoma of the gallbladder in 3 livers, of the pancreas in 2, of the hepatic ducts in 2, of the stomach in 2 and of the breast in 1. Metastases were found in 7 of these livers. As table 1 shows, a considerable increase of serum bilirubin and of alkaline phosphatase was present in all cases in which these determinations were carried out.

TABLE 1.—*Obstructive Jaundice*

Case	Diagnosis	Age, Yr.	Blood Findings	Alkaline Phosphatase in Bile Capillaries
1	Carcinoma of gallbladder	67	Severe jaundice—no data available	Moderately increased, but not uniformly
2	Carcinoma of pancreas	65	Icteric index 80; alkaline phosphatase 19 Bodansky units	Uniformly markedly increased
3	Carcinoma of gallbladder	74	Icteric index 57	Markedly increased, but not uniformly
4	Carcinoma of gallbladder	74	Icteric index 95; alkaline phosphatase 14 Bodansky units	Not increased
5	Carcinoma of breast	54	No data available	Uniformly increased
6	Carcinoma of common bile duct	53	Icteric index 60; alkaline phosphatase 31 King-Armstrong units	Not increased
7	Carcinoma of hepatic duct	65	Icteric index 80; alkaline phosphatase 36 King-Armstrong units	Moderately but not uniformly increased
8	Carcinoma of stomach	52	Severe jaundice—no data	Markedly uniformly increased
9	Carcinoma of stomach	52	Alkaline phosphatase 51 King-Armstrong units	Markedly uniformly increased
10	Carinoma of pancreas	74	Icteric index 21; alkaline phosphatase 16 King-Armstrong units	Moderately increased, but not uniformly

The cytoplasm of the liver cells showed little or no increase in alkaline phosphatase. The necrotic cells occasionally seen contained normal amounts of enzyme except in 2 specimens in which the reaction was stronger. In several livers the bile capillaries revealed considerable dilatation. In many fields they showed considerable widening of the stained zone (fig. 3). Such changes in the bile capillaries were uniform in 4 livers while in 1 they were marked in some fields and not present in others. Only moderate and not uniform increase in phosphatase activity of bile capillaries was seen in 3 and no increase in the remaining 2 livers. In several obstructed livers the sinusoids presented a prominent staining reaction, a phenomenon observed in the livers of dogs with experimental obstruction of the common bile duct. Infiltrating lymphocytes showed a varying degree of activity. Bile pigment as well as bile thrombi appeared green in these sections. Occasionally

bile thrombi took a dark stain. This was not due to phosphatase activity, however, since in control sections the same color was seen.

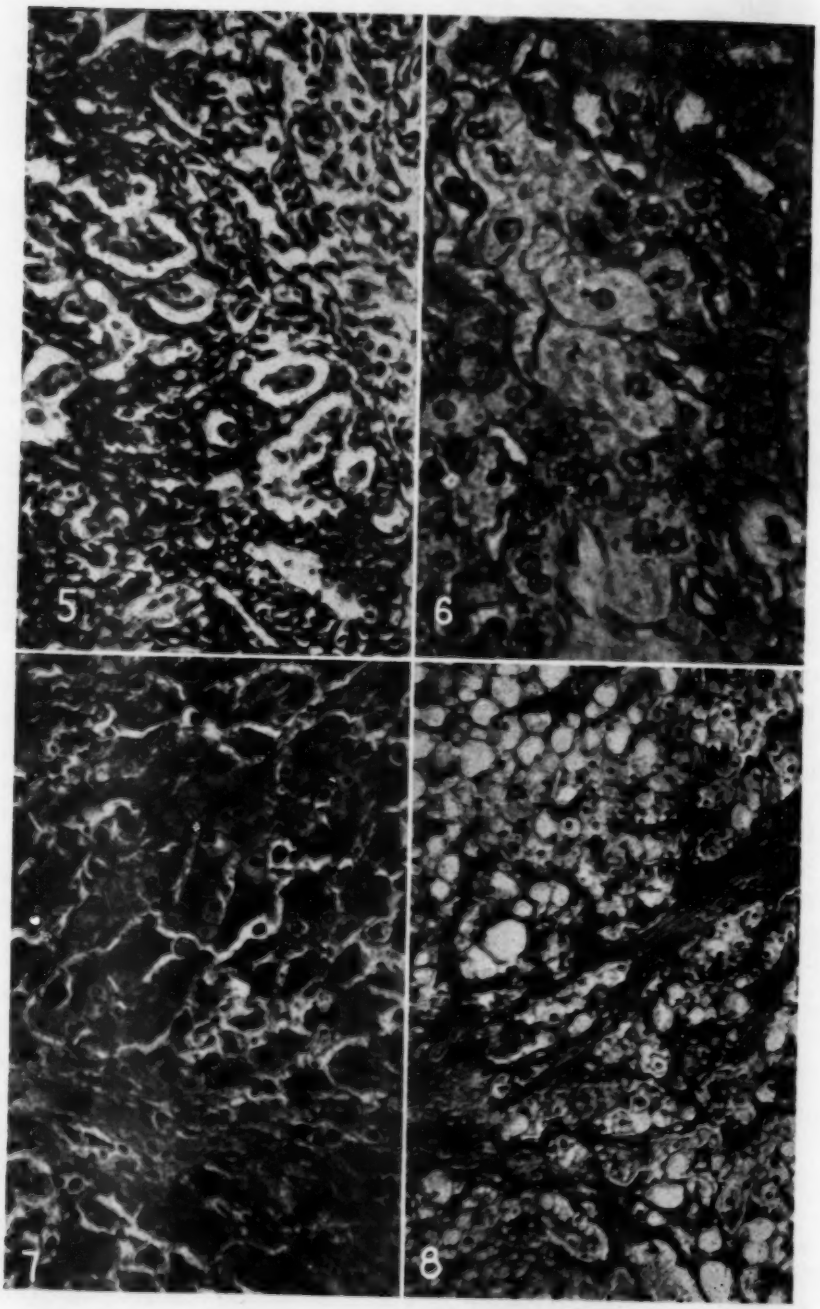
Some phosphatase activity was seen in the cells composing the metastatic tumor tissue. It was seen mostly in the chromatin and the nuclear membrane and only occasionally in the cytoplasm.

LIVER CELL NECROSIS

Three livers showing extensive acute necrosis of the hepatic cells and 4 with focal acute changes were studied. One liver with subacute yellow atrophy and another showing subacute hepatitis, from a patient with pernicious anemia, were included. In none of these livers was there an appreciable increase of alkaline phosphatase in the remaining undamaged liver cells. The necrotic cells did not show an increase in enzymatic activity (fig. 4). Occasionally, these cells were somewhat more stained, but proper evaluation could not be made since they were frequently shrunken. Some contained a dark pigment. This at first gave the impression of increased phosphatase activity, but the granules stained in control sections did not signify this. Infiltrating leukocytes, lymphocytes and plasma cells showed a varying degree of activity. Bile capillaries between remaining liver cells were, for the most part, devoid of phosphatase activity. In necrotic areas, most of the walls of the sinusoids retained their activity. In the 2 livers with subacute inflammation, prominent activity was exhibited by proliferating fibroblasts and infiltrating lymphocytes (fig. 5); in one specimen there was marked activity of the bile capillaries, while in the other they took the stain only faintly. A patient who died two days after extensive burns had clusters of hydropic cells in the liver. These showed much less phosphatase than the adjacent liver cells. However, this may have been due to the distention of cells and may therefore not have represented an actual decrease in phosphatase activity (fig. 6). Cells of this kind occurring after experimental poisoning with chloroform and carbon tetrachloride show a similar behavior [1a]

FATTY LIVER

Fatty changes were present in a number of specimens. In several only occasional fat droplets were seen, while in others, these changes were extensive. Phosphatase activity was missing in the location where the fat droplets had been present (figs. 4 and 8). There was no accumulation of phosphatase in the remaining cytoplasm. The nuclei and walls of the sinusoids showed activity to the same extent as those in control sections. The appearance of liver cells containing fat was identical with that previously described in various experimental conditions.[1a] Whether the disappearance of the enzyme seen in these preparations of fatty livers constitutes a real decrease can be determined



FIGURES 5 TO 8

(See legends on opposite page)

only with chemical methods. It is possible, although unlikely, that phosphatase somehow bound to the fat is removed together with the fat during the process of fixation and embedding.

CIRRHOSIS OF THE LIVER

Sections of 8 livers with Laennec cirrhosis, 2 with hypertrophic cholangiolitic cirrhosis, 2 with toxic cirrhosis and 1 with obstructive biliary cirrhosis were examined. In several of these organs there was also hepatocellular damage of recent origin. These patients had increases of bilirubin and phosphatase in their serum (table 2).

TABLE 2.—*Cirrhosis of the Liver*

Case	Diagnosis	Age, Yr.	Blood Findings
1	Laennec cirrhosis and hepatitis	49	Jaundice—no data
2	Laennec cirrhosis and hepatitis	69	Icteric index 80
3	Laennec cirrhosis and cancerous hepatoma	60	Alkaline phosphatase 33 King-Armstrong units
4	Laennec cirrhosis and hepatitis	46	Alkaline phosphatase 28 King-Armstrong units, icteric index 39
5	Laennec cirrhosis and hepatitis	55	Alkaline phosphatase 16 King-Armstrong units, icteric index 60
6	Laennec cirrhosis	65	No jaundice—no data available
7	Laennec cirrhosis	71	Alkaline phosphatase 13 King-Armstrong units, icteric index 6
8	Laennec cirrhosis		
9	Hypertrophic cholangiolitic cirrhosis	42	Alkaline phosphatase 18 King-Armstrong units, icteric index 6
10	Hypertrophic cholangiolitic cirrhosis	47	Icteric index 16
11	Toxic cirrhosis	10	Alkaline phosphatase 29 King-Armstrong units, icteric index 27
12	Toxic cirrhosis	11	Alkaline phosphatase 13 King-Armstrong units, icteric index 90
13	Obstructive biliary cirrhosis (14 years after traumatic laceration of common bile duct)	69	Alkaline phosphatase 49 King-Armstrong units

In most of the undamaged liver cells alkaline phosphatase activity was normal. There was no increase of the enzyme in necrotic cells. In some of the livers, there was a considerable increase of enzymatic

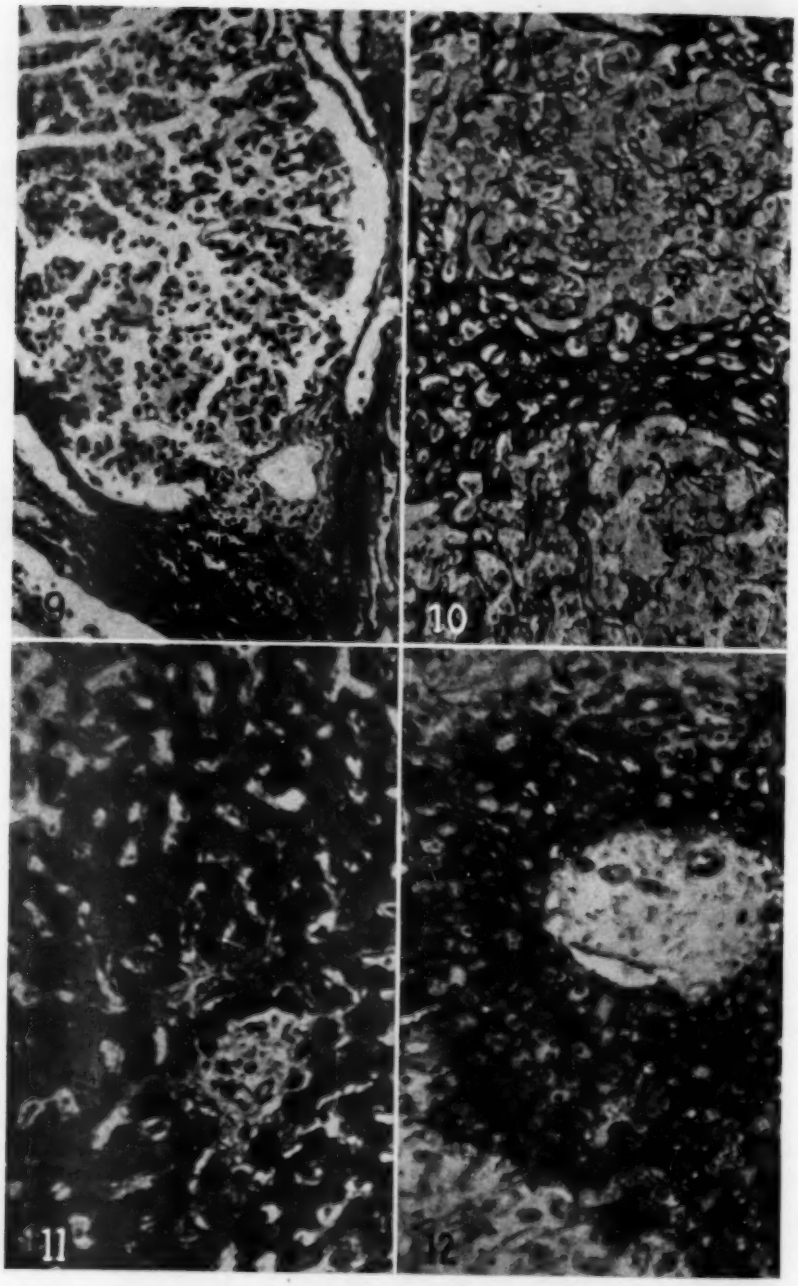
EXPLANATION OF FIGURES 5 TO 8

Fig. 5.—Alkaline phosphatase activity in the liver of a patient with subacute yellow atrophy of the liver. There is conspicuous activity in the proliferating connective tissue and the inflammatory cells. The remaining liver cells show a normal amount of phosphatase. × 125.

Fig. 6.—Alkaline phosphatase activity in the liver of a patient who died because of extensive burns. Hydropic liver cells show apparently a decrease in enzymatic activity. × 180.

Fig. 7.—Alkaline phosphatase in the liver of a patient with Laennec's cirrhosis and superimposed hepatocellular damage. There is considerable activity in some of the bile capillaries. × 125.

Fig. 8.—Alkaline phosphatase in the liver of a patient with Laennec's cirrhosis in a fatty stage. The proliferating connective tissue reveals phosphatase activity. The liver cells infiltrated by fat are devoid of enzymatic activity. × 125.



FIGURES 9 TO 12

(See legends on opposite page)

activity in the bile capillaries, and occasionally in the cytoplasm of cells surrounding those capillaries there was an increase (fig. 7). Similar to the observations in obstructive jaundice, this increase was not uniform. There was considerable variation in the activity of the connective tissue separating the pseudolobules. The infiltrating lymphocytes contained a varying amount. Phosphatase activity was decreased in fat-containing cells (fig. 8).

There was 1 liver with cancerous hepatoma in association with Laennec's cirrhosis. The amount of alkaline phosphatase activity in the tumor cells was similar to that in normal livers. Phosphatase was localized mainly in the chromatin and the nuclear membrane; the cytoplasm contained little (fig. 9). A normal distribution of phosphatase was also seen in 2 livers with benign adenoma.

In 2 livers hypertrophic cholangiolitic cirrhosis, and in 1 liver obstructive biliary cirrhosis, was found. The picture in each of these was not different from typical Laennec cirrhosis. So-called "bile duct sprouts" in the connective tissue separating the pseudolobules did not show much activity. The 2 livers with toxic cirrhosis showed conspicuous activity in the proliferating connective tissue and the infiltrating lymphocytes (fig. 10); in one, bile capillaries showed occasional dilatation, while in the other some of the liver cells showed an increased amount of cytoplasmic phosphatase activity.

LEUKEMIA

Livers from 4 patients with acute and 2 with chronic myeloid leukemia as well as from 1 with chronic lymphatic leukemia and 1 with lymphosarcomatosis were studied. In 2 organs a diffuse moderate increase of cytoplasmic phosphatase activity was seen. Otherwise, in distribution and amount of cytoplasmic activity the sections were similar to the control sections. Infiltrating leukemic cells showed moderate phosphatase activity, especially in the nuclei.

EXPLANATION OF FIGURES 9 TO 12

Fig. 9.—Alkaline phosphatase in the liver of a patient with hepatic carcinoma. In distribution and amount of enzymatic activity the tumor cells are similar to normal liver cells. The surrounding connective tissue is very active. × 100.

Fig. 10.—Alkaline phosphatase in the liver of a patient with toxic cirrhosis. There is conspicuous activity of the proliferating connective tissue, while the liver cells show a normal distribution. × 125.

Fig. 11.—Alkaline phosphatase in the liver of a patient with moderate chronic passive congestion of the liver. There is diffuse increase in cytoplasmic phosphatase. × 125.

Fig. 12.—Alkaline phosphatase in the liver of a patient with severe passive congestion of the liver. There is conspicuous activity in the bile capillaries of the undamaged cells in the periportal fields, while the centrally located damaged cells show a lessened amount of enzymatic activity. × 100.

INCREASE IN CYTOPLASMIC PHOSPHATASE

An increase in cytoplasmic alkaline phosphatase was found in the livers of 12 patients who died of various diseases. Jaundice was absent in each instance. Three of the patients died of cardiac failure, 1 of lymphosarcomatosis, 1 of acute leukemia, 1 of carcinoma of the esophagus, 1 of carcinoma of the hepatic flexure, 2 of chronic nephritis, 1 of bleeding peptic ulcer, 1 of influenzal laryngotracheitis and 1 of diabetes mellitus and syphilitic aortitis. The increase in cytoplasmic phosphatase activity after fourteen hours of incubation was only moderate in some instances, quite striking in others (fig. 11). In several livers many of the bile capillaries showed increased phosphatase.

There was an increase in the phosphatase activity of the cytoplasm in a number of livers with chronic congestion, in others not. Where there was an increase it may not have been real but apparent; the appearance may have been due to condensation of the cytoplasmic constituents secondary to pressure. In the livers showing chronic congestion the sinusoidal walls were not infrequently separated from the liver cells and stained as fine black lines.

COMMENT

Since Gomori [2] and Takamatsu [6] demonstrated a histochemical method for the visualizing of alkaline phosphatase activity in tissue sections a number of papers have been published by investigators employing this method. The manner in which alkaline phosphatase is distributed in the normal organs of different species has been established.[7] Interesting observations have been made concerning the appearance of phosphatase in the developing embryo,[8] the fetal membranes and the placenta.[9]

It has been established that under various experimental conditions changes in alkaline phosphatase activity occur, especially in the kidney [10] and the liver.[1] However not many observations have been made on human material. The distribution of the enzyme in normal organs as demonstrated with the microtechnical method has been described by Takamatsu [6] Gomori [7a] and Kabat and Furth.[3] That in the nervous

6. Takamatsu, H.: Tr. Soc. path. jap. **29**:492, 1938.

7. (*a*) Gomori, G.: J. Cell. & Comp. Physiol. **17**:71, 1941. (*b*) Bourne, G.: Quart. J. Exper. Physiol. **32**:1, 1943. (*c*) Kabat and Furth.[3]

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system has been described by Landow, Kabat and Newman.[11] This enzyme has also been studied in neoplasms.[12] Marked decrease of the enzymatic activity of diseased kidneys was noticed by Gomori.[12b] Takamatsu[6] stated that damaged liver cells contain increased amounts of phosphatase, without giving further details.

The present report concerns an attempt made to study the distribution of alkaline phosphatase in the livers of postmortem material, It is obvious that organs of patients who have died of various diseases are not in the same state of preservation as are the organs of experimental animals. Although even forty-eight hours after death no significant changes are seen in the amount and the distribution of enzymatic activity in normal animal organs, it is possible that during the agonal phase in man changes in enzymatic activity may take place. This is particularly true for the liver, in which postmortem changes occur sometimes very rapidly. We wish to emphasize these possible sources of error. The number of postmortem examinations of livers is comparatively small and will have to be supplemented by more biopsies. Such a study of fatty and cirrhotic livers of patients with pellagra has been announced by Gillman and Gillman.[13] However, even considering all the obvious difficulties, we see an encouraging feature in the fact that changes occurring in human livers under conditions of disease resemble those occurring under similar experimental conditions.

The distribution in the normal human liver was found similar to that demonstrated by Gomori.[7a] It resembled the picture seen in the livers of various animals, although, naturally, in the organs of normal animals the results are more uniform. This applies particularly to the activity in sinusoids and bile capillaries. Phosphatase activity of the latter was more regularly seen in the rabbit and the dog. It was also found distinct in some of the normal human livers. Further investigation will have to establish whether the varying activity of the bile capillaries is due to varying functional stages.[14]

Interpretations of the increased phosphatase activity in some of the livers offer difficulties so long as no correlated chemical studies are carried out. While the staining methods for the demonstration of alkaline phosphatase permit its localization, quantitative changes are more difficult to interpret. An impressive increase of the staining reaction occurring in the cytoplasm under otherwise identical conditions is sug-

11. Landow, H.; Kabat, E. A., and Newman, W.: Arch. Neurol. & Psychiat. **48**:518, 1942.

12. (*a*) Gomori, G.: Am. J. Path. **19**:197, 1943; (*b*) J. Mt. Sinai Hosp. **11**:317, 1945. (*c*) Landow and others.[11] (*d*) Kabat and Furth.[3]

13. Gillman, J., and Gillman, T.: Arch. Path. **40**:239, 1945.

14. Forsgren, E.: Skandinav. Arch. f. Physiol. **55**:144, 1929; J. Morphol. **47**: 519, 1929.

gestive of a real increase of enzymatic activity. Such an increase has been observed in the livers of mice fed starvation and protein-deficient diets and to a lesser degree in rats.[1a] It is probable that this increase signifies an intensification of metabolic processes which requires a greater amount of phosphatase.

The findings in necrotic liver cells are in general in good agreement with the previously reported experimental findings. It was seen that in livers damaged by chloroform, carbon tetrachloride and phosphorus the necrotic liver cells did not show a significant increase in enzymatic activity.[1a] Only in occasional specimens among the human livers was phosphatase activity of necrotic liver cells increased. Mostly it was normal or even decreased.

In the livers with biliary obstruction accentuation of the bile capillaries was marked in some, moderate in others and completely missing in still others. Not in a single instance, however, was the increase in phosphatase activity in bile capillaries as conspicuous as that seen in the canine liver after ligation of the common bile duct.[1b] While in some livers enzymatic activity was obviously increased in the cytoplasm in the close vicinity of the bile capillaries, there occurred only little increase in the remaining cytoplasm. The fact that in several livers no increased activity of the bile capillaries could be found is of particular interest. Since such a behavior was also observed in one biopsy specimen, which was immediately fixed in acetone, postmortem changes can be excluded. It seems probable that the liver cells in these instances have lost their ability to take up phosphatase from the blood stream. Animal experiments dealing with this problem are in progress.

In livers showing hepatocellular damage a varying behavior of phosphatase activity in bile capillaries was observed. In several with extensive necrosis of liver cells no stainable capillaries could be made out, while in others, including some in which damage of liver cells was superimposed on preexisting cirrhosis, a varying amount of the bile capillaries showed prominent activity. Such widening of bile capillaries may be caused by intrahepatic obstruction due to hepatocellular dysfunction. However, a considerable increase in phosphatase activity in bile capillaries may occur without obvious cause, as illustrated in the following case: A 54 year old man died because of occlusion of the right coronary artery with subsequent myomalacia and perforation of the interventricular septum. The liver showed severe passive congestion. The cells in the centrally congested fields showed decreased enzymatic activity, while the remaining undamaged liver cells in the periphery showed considerable increase in enzymatic activity of the bile capillaries (fig. 12). The remaining cytoplasm showed normal amounts of phosphatase. Clinically and at autopsy jaundice was not present. In none of the other livers in which severe congestion occurred were similar changes seen.

Metastatic tumor tissue showed activity mostly in the nuclei. Kabat and Furth [3] did not notice any activity in the tumor cells in cases of carcinoma of the breast, the stomach and the large intestines and hypernephroma. The moderate activity seen in our sections is obviously due to the fact that they were incubated longer in the substrate mixture. Phosphatase activity was also seen in the nuclei of a primary carcinoma of the liver and in those of two benign adenomas and to a lesser degree in the cytoplasm, resembling that observed in normal liver. Among animals, marked increase of phosphatase activity was found in the cancerous hepatoma of the rat, while the hepatoma of the mouse showed a decreased amount.[15]

The liver cells in various forms of cirrhosis showed preponderantly a normal activity of phosphatase. Occasional cells, which were located in the vicinity of bile capillaries showing conspicuous activity, revealed some increase in cytoplasmic activity. The considerable increase in phosphatase noticed in adenomatous areas in the experimental dietary cirrhosis of the rat [16] was not seen in human livers. A prominent feature in 2 livers showing toxic cirrhosis as well as in several with Laennec's cirrhosis was the considerable activity of the proliferating connective tissue. This was also seen in 2 livers with subacute diffuse hepatitis. The great activity of the young connective tissue of the rat's liver was first described by Fell and Danielli.[16] In cases of cirrhosis the conspicuous amount of phosphatase presumably signifies a still active growth of connective tissue, while its absence is indicative of a quiescent stage.

In the livers of 7 patients who died of leukemia and of 1 who had lymphosarcomatosis, the infiltrating cells showed a varying degree of moderate phosphatase activity. Previously, absence of phosphatase activity had been found in the immature myeloid cells both of leukemic and normal persons, observed in bone marrow and peripheral blood, and a considerably lessened activity in the mature cells of patients with chronic myeloid leukemia.[17] A different behavior was observed in the staining reaction of lymphocytes in blood films and tissue sections. While in blood films lymphocytes were consistently devoid of phosphatase, in lymph nodes and also in chronic inflammatory foci they showed activity of a varying degree. A similar observation had been previously made by Gomori. The reason for this difference is obscure. However, it is unlikely that the difference was due to the fact that the examinations were carried out on different preparations, since in cases of

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16. Fell, H. B., and Danielli, J. F.: Brit. J. Exper. Path. **24**:196, 1943.

17. Wachstein, M.: J. Lab. & Clin. Med. **31**:1, 1946.

infection polymorphonuclear leukocytes show conspicuous activity both in tissue sections and in blood films.

The source of the increased amount of serum alkaline phosphatase is still controversial.[18] One theory maintains that the damaged liver releases a phosphatase-activating substance which accounts for the rise in enzymatic activity. This has been disproved.[19] According to another theory,[20] the damaged liver cells may produce an increased amount of phosphatase. In conformity with the behavior of necrotic liver cells under experimental conditions, there is no significant increase of phosphatase in disintegrating liver cells of man. The amount of enzymatic activity is small both in normal and in necrotic liver cells.

Experimental evidence brought forward by several authors[21] supports the third theory that a rise in alkaline phosphatase is due to the inability of the liver cells to excrete the enzyme. This view is shared by Gutman and co-workers on the basis of clinical evidence.[22] We believe that the pictures in human livers stained for alkaline phosphatase activity can best be explained on the basis of this theory. In patients with obstructive jaundice, considerable retention of the enzyme in the bile capillaries occurs, although it never reaches the extent seen in dogs with biliary obstruction. The fact that this activity was absent in several cases of obstructive jaundice, as well as the irregularity in which such retention was seen in hepatocellular damage, strongly suggests that the functional state of the liver cells is of great importance for the excretion of the enzyme. It is probable that the liver cells which are damaged too severely lose their ability to take up the enzyme from the blood and excrete it. Sharnoff and co-workers,[23] on comparing the hepatic tissue changes in human postmortem material and changes in serum alkaline phosphatase activity, concluded that the degree of injury of hepatic cells was the factor determining the rise of serum alkaline phosphatase. That the functional state of the hepatic cells is important for the excretion of alkaline phosphatase is further strongly supported by the findings of considerable increases in serum alkaline

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23. Sharnoff, J. G.; Lisa, F. R., and Riedel, P. A.: Arch. Path. **33**:460, 1942.

phosphatase in dogs fed choline-deficient diets. The increase in enzymatic activity in the blood serum is concomitant with the impairment of the liver function, as proved by various tests,[24] but is not accompanied by jaundice. The histologic picture of these livers is characterized by severe fatty changes.[25]

On the basis of the behavior of alkaline phosphatase activity in the liver the increase in serum phosphatase occurring in hepatic diseases can best be explained in the following way: The parenchymal cells are unable to excrete the enzyme either because of external obstruction or because of inability to take up phosphatase from the blood or because of a combination of both factors.

However, it should be remembered that alkaline phosphatase can be excreted in additional ways. It can leave the body in the pancreatic juice,[26] through the intestines,[27] and, in some species, through the kidneys.[28] Severe disturbance of the calcium and phosphorus metabolism occurring in hepatic diseases can in turn influence the production of bone phosphatase.[29] These extrahepatic factors are probably of considerable importance. They may explain the peculiar behavior of serum alkaline phosphatase in certain conditions, such as congenital atresia of the bile ducts, in which there is a normal amount of this enzyme in the serum.

SUMMARY

Alkaline phosphatase activity was studied in sections of livers of human postmortem material. A fairly regular distribution was found in livers from patients who had died from various diseases not involving the liver itself. Considerable increase of enzymatic activity was seen in bile capillaries in the livers of several of the patients having obstructive jaundice. Increased activity was seen in the bile capillaries also in some of the livers with heptocellular damage but not regularly. Necrotic liver cells showed no significant increase of enzymatic activity. Considerable activity was seen in the proliferating connective tissue in livers of patients with subacute hepatitis and patients with toxic cirrhosis and in the livers of some of the patients with Laennec's cirrhosis. Meta-

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static as well as primary tumor tissue showed moderate phosphatase activity of the nuclei. Infiltrating leukemic cells showed some phosphatase activity of the nuclei. In some of the livers which were not involved primarily by diseases, considerable increases of cytoplasmic phosphatase activity occurred. The behavior of phosphatase revealed in these sections favors the assumption that the increase of serum alkaline phosphatase in cases of damage of the liver is due to retention of the enzyme in the blood. The inability of the liver to excrete it may be caused by external obstruction or by cellular dysfunction. The importance of extrahepatic factors, however, should not be underestimated.

GRANULAR CELL MYOBLASTOMA

ELIZABETH B. POWELL, M.D.
HOUSTON, TEXAS

MUCH HAS been written in recent years about a group of tumors most frequently designated by the names "granular cell myoblastoma," "myoblastic myoma," "myoblastoma" and "rhabdomyoma." In 1924 Klemperer [1] reviewed the literature and reported 50 cases of "myoblastoma of striated muscle." Howe and Warren [2] in 1944 brought the review of the literature up to date and made a thorough analysis of 114 additional cases. Since then, new cases have been reported by Hartz,[3] Ravich, Stout and Ravich [4] and Crane and Tremblay.[5]

The distribution of the sites of these tumors is rather diffuse. Converting the figures of Crane and Tremblay [5] into percentages, one finds that 37.6 per cent of the reported sites of myoblastoma were in the tongue, while 20.4 per cent were in the skin and the subcutaneous tissue. The others were in the following tissues in descending order of incidence: muscle, maxilla, breast, larynx, vocal cord, mandible, lip, trachea, bronchus, ear and alveolar process.

The various authors are fairly well agreed on the histologic characteristics of tumors of this group. Two types of cells are described. Cells of the first type are large, pale, granular and polyhedral or ovoid. Those of the second type are larger, elongated and finely granular and are arranged in ribbon-like syncytial masses. Cross and longitudinal striations have been observed in some of these cells. The cytoplasm tends to be acidophilic, but Horn and Stout [6] reported great variation in the number, the size, the density and the depth of acidophilic staining of the characteristic granules. This may cause difficulty in diagnosis, especially when combined with a so-called organoid pattern of growth. In this pattern the cells have a pseudoalveolar arrangement frequently near or around thin-walled blood vessels, giving the growths a strong resemblance to tumors arising from endocrine glands.[7] The nuclei are

From the Department of Pathology, Baylor University College of Medicine.

1. Klemperer, P.: Am. J. Cancer **20**:324, 1934.
2. Howe, C. W., and Warren, S.: Surgery **16**:319, 1944.
3. Hartz, P. H.: Am. J. Clin. Path. **14**:582, 1944.
4. Ravich, A.; Stout, A. P., and Ravich, R. A.: Ann. Surg. **121**:361, 1945.
5. Crane, A. R., and Tremblay, R. G.: Am. J. Path. **21**:357, 1945.
6. Horn, R. C., and Stout, A. P.: Surg., Gynec. & Obst. **76**:315, 1943.
7. Horn and Stout.[6] Hartz.[3]

described as fairly regular, small, dense, with rare mitoses. The stroma is composed of fine strands of connective tissue, which supports either single cells or groups of cells. Some of these tumors are surrounded by a definite capsule, but the majority are nonencapsulated and infiltrating.

To date there is no agreement or any conclusive evidence in the literature concerning the exact origin of myoblastoma. Opinion seems to lean toward Klinge's [8] dysontogenetic theory, which states that tumors of this group arise from retained or misplaced primitive myoblasts which failed to develop into adult muscle tissue. Abrikossoff,[9] in reporting the first cases of myoblastoma, interpreted the tumors as arising from primitive muscle cells which developed in an attempt to repair a degenerative process following injury or inflammation, not from embryonal cell rests. Later he conceded that myoblastoma arising in an area devoid of striated muscle might originate from primitive myoblasts representing an embryologic rest. Gray and Gruenfeld [10] maintained that convincing evidence is lacking of the uniformly myogenous nature of various intracutaneous, submucous, intramuscular and lingual tumors described as myoblastoma. They accepted the myogenous nature of the cells in lingual tumors but expressed the belief that these lesions are the result of a degenerative process in skeletal muscle. However, they could not explain the proliferation or the invasiveness of the tumor cells. Some observers noted the xanthomatous appearance of myoblastoma, but special stains failed to reveal the presence of fat in the cells. Due to the granularity of the cytoplasm, the tumors have been described as "storage cell tumors" arising from muscle cells or undifferentiated mesenchyme.[11] The possibility that the large granular cells may be histiocytes prompted Tuta and Schmidt [11] to use various staining methods to determine the nature of the cytoplasmic granules. They thought that glycogen and a mucin-like substance may have been present in the cytoplasm of the cells in question. Their results were not conclusive, since the tissue had not been properly fixed in absolute alcohol.

Granular cell myoblastoma is considered to be a benign tumor. However, Howe and Warren [2] reported a total of 14 cases in which it showed cancerous characteristics, but in only 3 of these were metastases demonstrated. This was followed by a report from Ravich, Stout and Ravich [4] of a cancer of the bladder which was diagnosed as granular cell myoblastoma and which recurred after excision. At autopsy, extensive metastases were found, notably in the liver, the spleen, the lung, the

8. Klinge, F.: Verhandl. d. deutsch. path. Gesellsch. **23**:376, 1928.
9. Abrikossoff, A.: Virchows Arch. f. path. Anat. **260**:215, 1926.
10. Gray, S. H., and Gruenfeld, G. E.: Am. J. Cancer **30**:699, 1937.
11. Tuta, J. A., and Schmidt, F. R.: Arch. Dermat. & Syph. **46**:225, 1942.

skull and the pelvic tissues. Local recurrences following incomplete removal have been reported by Horn and Stout [6] and Cappell and Montgomery.[12] According to Howe and Warren [2] when a myoblastoma shows (1) atypism of cells, (2) an excessive number of mitotic figures, (3) a spindle cell or sarcomatous pattern and (4) local invasion, it should be treated surgically as a cancer, especially if the patient is over 50 years of age.

REPORT OF CASES

CASE 1.—During the course of a routine physical check-up, Mrs. F. J., a 49 year old white woman, was found to have a small painless nodule in the skin over the right scapula. This tumor was excised on May 2, 1944. The scar was inspected on June 19, 1946, and there was no evidence of recurrence.

The gross specimen consisted of an elliptic piece of skin, measuring 4 by 2.5 cm., with underlying subcutaneous tissue attached. In the center of this mass of tissue was a nodule measuring 1.7 cm. in diameter. The skin overlying the nodule was coarse and slightly roughened. On section the nodule was rather firm in consistency, yellowish gray and poorly circumscribed. Microscopic sections showed it to be composed of cells typical of granular cell myoblastoma. The squamous epithelium was slightly thickened over the mass. The tumor cells extended up to the basal layer of the epithelium but did not invade it. The entire corium except for a few hair follicles, sweat glands and bundles of collagen fibers was replaced by a fairly compact tumor, which possessed a fine connective tissue stroma. The tumor cells were elongated and polygonal, with an abundance of cytoplasm, which was pink staining and diffusely granular. The nuclei were small, round, pale staining and centrally located, without evidence of mitotic figures. Tumor cells were present deep in the subcutaneous fat. Occasionally, the cells had a vacuolated, foamy appearance suggestive of xanthoma cells, but special stains failed to reveal the presence of fat.

CASE 2.—E. N., a 60 year old Negro woman, was seen on March 22, 1944, because of a nonpainful tumor of the right breast. Her only complaint was of itching of the skin over this tumor. Examination of the breast revealed a mass in the upper and outer quadrant. The tumor was not attached to the underlying tissue but was definitely attached to the skin, which was discolored in this area. There were no palpable axillary nodes. Simple mastectomy was done on March 23. The patient was last seen on Aug. 16, 1945, and there was no evidence of recurrence.

Only a portion of the breast was submitted for pathologic examination. It measured 8 by 5 by 4 cm. and was composed mostly of fatty tissue covered by pigmented skin. Included was a tumor mass, measuring 2.5 cm. in diameter. It was gray, firm, fairly well demarcated but not encapsulated. It was adherent to the skin. Microscopic sections showed the tumor to be composed of oval or polygonal cells, which were large and pink staining and contained an abundance of finely granular cytoplasm. The nuclei were small, deep staining and regular. The cellular outlines were indistinct in areas, and in other areas there was a pseudoalveolar pattern. Occasional ribbon-like syncytial arrangements of cells were also seen. Tumor cells extended up to the thin, normal-appearing squamous epithelium of the skin. Scattered throughout the mass were small collections of

12. Cappell, D. F., and Montgomery, G. L.: J. Path. & Bact. **44**:517, 1937.

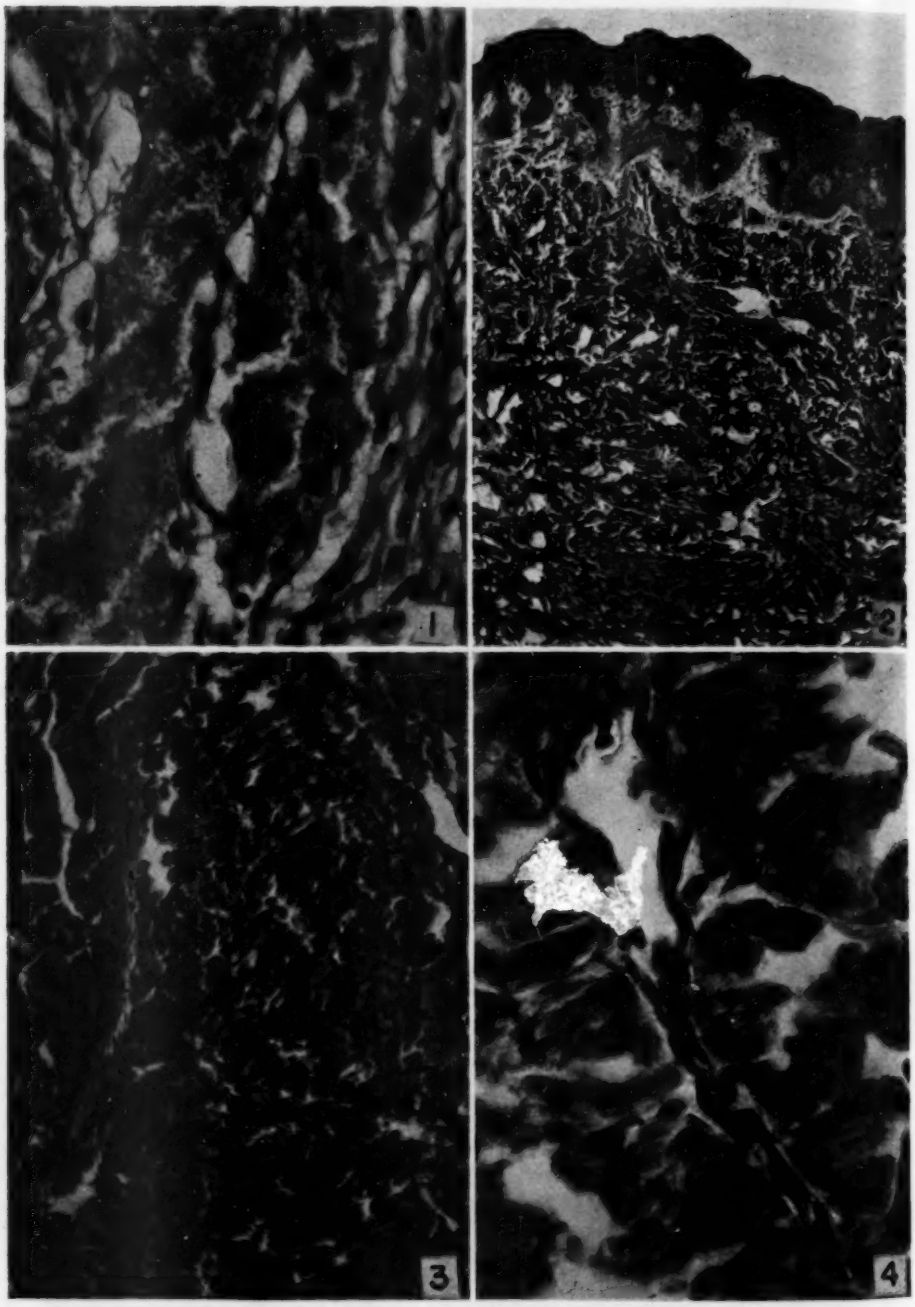

Fig. 1 (case 2).—Cells of the tumor of the breast showing granularity of the cytoplasm and syncytial arrangement. × 550.

Fig. 2 (case 1).—Low power view showing the characteristic hyperplasia of the epidermis. × 122.

Fig. 3 (case 3).—An area in the tumor mass of the tongue showing the alveolar arrangement of the cells. × 122.

Fig. 4 (case 3).—Same as figure 3. × 550.

lymphocytes and occasional ducts. No definite stainable fat could be demonstrated in the tumor cells.

CASE 3.—J. L. C., a 14 year old Negro youth, was first seen on Aug. 22, 1944, complaining of a painless growth located between the teeth and the tongue on the left side of his mouth, of four months' duration. Three months previously he noted that it interfered with his speech. Two years before the appearance of the growth he noticed a swelling, which was painless, below the left side of his jaw. Physical examination showed a mass arising between the tongue and the teeth on the left side, which extended to the right side of the floor of the mouth and displaced the tongue to the right. There was also a hard swelling under the left mandible, extending down into the neck. Biopsy was done on August 22 and on September 1. He was again seen on October 3, at which time excision of the tumor was considered but was not done. On his last admission, November 18, he complained of bleeding from under the tongue of four weeks' duration. On the day of admission the bleeding became profuse. Examination showed the site of the previous biopsy under the tongue to be granular, bleeding and apparently necrotic. Sterile cotton was packed under the tongue to control the bleeding, but this measure proved inadequate. In spite of blood transfusion and intravenous injection of fluids, his condition grew worse, and bleeding continued. Finally, November 24, the left external carotid artery was ligated, with the patient under pentothal sodium anesthesia. Following the operation, the patient had two attacks of respiratory failure, which were treated by artificial respiration and administration of respiratory stimulants. The respirations then became fairly regular, but the patient never regained consciousness. He died nine hours after the operation.

At autopsy the tongue, with tumor attached, was removed. The omohyoid muscle was almost completely destroyed by the growth, which seemed to arise from the under surface of the tongue near the base. The tumor measured 8 by 6 by 4 cm., was firm and rubbery in consistency and involved the entire under surface of the tongue except for a 2 cm. portion near the tip. There was an extensive erosion of the under surface of the tongue and the tumor proper. The walls of the resulting cavity were soft, friable, ragged and necrotic. The tumor involved the alveolar margin of the gum and destroyed a portion of the mandible on the left side. Microscopic sections showed typical large ovoid or polygonal pink-staining cells with an abundance of coarsely granular cytoplasm and regular small nuclei. The nucleoli were enlarged and unusually prominent. The majority of the cells were arranged in an organoid pattern of groups of from four to six cells. These groups were surrounded by thin connective tissue containing small capillaries. There were suggestive attempts at formation of lumens. Occasional syncytial masses of tumor cells with indistinct cellular outlines were seen. There were invasion and destruction of the striated muscle of the tongue. In other areas the tumor was necrotic and heavily infiltrated by neutrophils and lymphocytes. At the margin of these necrotic areas were numerous large, thin-walled dilated vessels, which were engorged with blood. The pathologic diagnosis of the tumor was myoblastoma.

CASE 4.—G. H., a 26 year old Negro woman was first seen, Jan. 3, 1944, complaining of almost constant pain in the lower abdominal and pelvic regions of several years' duration. This pain had been increasing in severity, especially during her menstrual periods. The menses had been regular. She also complained of numerous nodules over her body, most of which had been present as long as she could remember. These nodules began as small pimples, causing no pain or discomfort other than slight itching. The skin over these masses had never

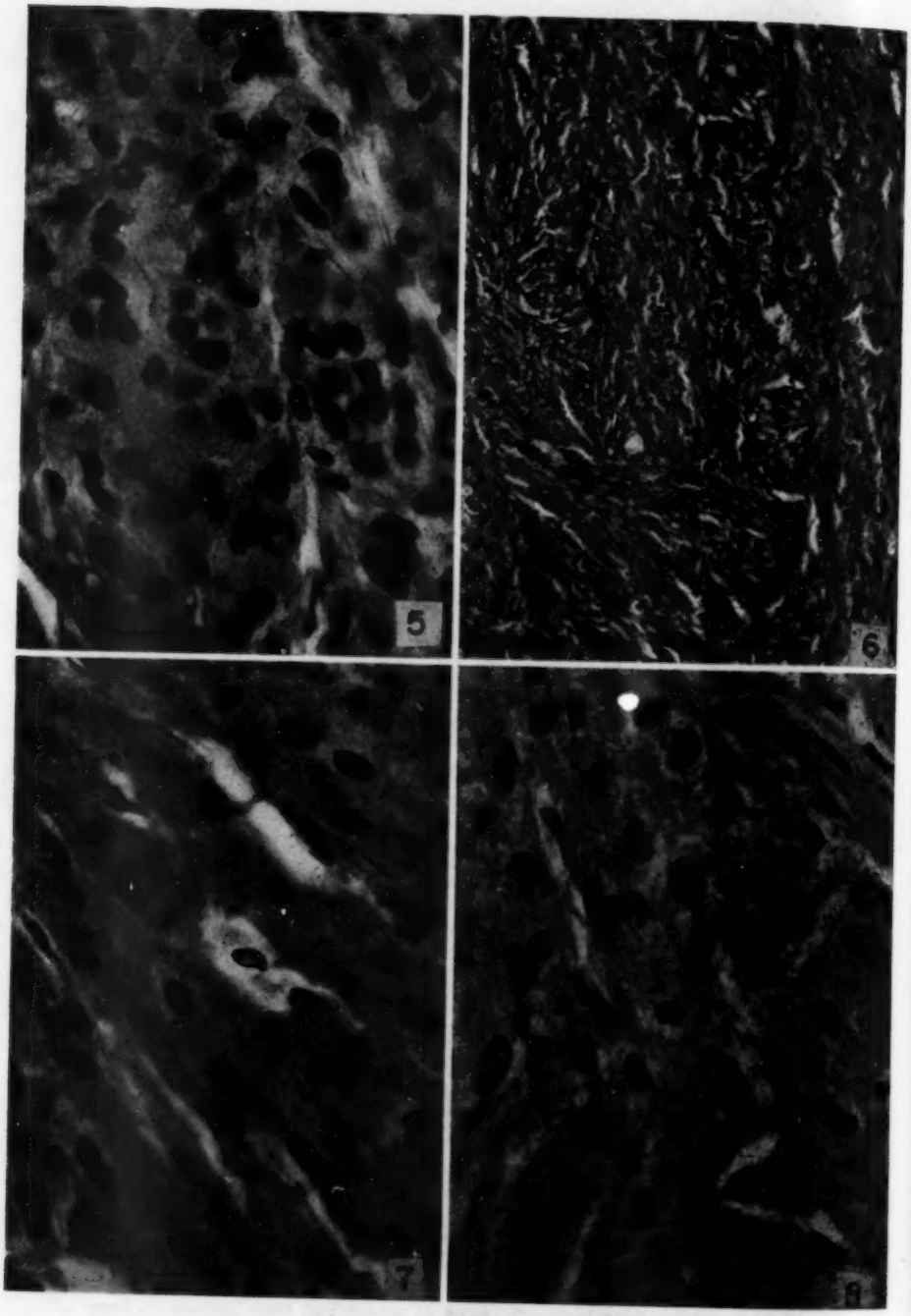

Figure 2

(See legend on opposite page)

become ulcerated or infected. Physical examination showed numerous firm subcutaneous nodules, which were freely movable except for their attachment to the skin. These masses were present in the scalp, an upper eyelid, the left side of the lower lip, the right axilla, the right lateral body wall above the pelvic brim, the left thigh and the vulva, between the shoulder blades, in the middle right toe and on the buttocks. They varied from a few millimeters to 4 cm. in diameter. On pelvic examination the positive findings consisted of a vaginal stricture, a cervical polyp and an enlarged, nodular uterus. The adnexa could not be made out. On January 4, tumor masses were removed from the left thigh, the vulva and the right axilla. Panhysterectomy and bilateral salpingo-oophrectomy were done January 13 with removal of a retroperitoneal tumor. The uterus was enlarged and contained several subserous growths, diagnosed as leiomyoma, the largest of which measured 4 cm. in diameter. The right ovary measured 6 by 6 by 5 cm. Except for a thin cortex, the organ had been completely replaced by a solid tumor mass, which had a soft, doughy feel. This mass was not encapsulated. The left ovary measured 5.5 by 4 cm. by 3 cm. It contained two tumor masses similar in gross appearance to that in the right ovary. The larger mass measured 4 by 3 cm. The smaller was 1 cm. in diameter. The retroperitoneal mass measured 7 by 6 by 3 cm. It had an irregular outer surface and was not encapsulated. On cut section its gross appearance was similar to that of the ovarian growth. In March 1945 a subcutaneous nodule was removed from the perineum. In the meantime several nodules had appeared over her body, none of which caused her any discomfort. She was seen on Oct. 20 and Nov. 30, 1945. On both of these occasions examination demonstrated that no pelvic masses were present.

On histologic study one was struck by the remarkable similarity of the tumor cells in the subcutaneous nodules, the ovarian tumors and the retroperitoneal mass. These were either spindle shaped, ovoid or polyhedral and fine to coarsely granular. The cutaneous and ovarian lesions showed a somewhat foamy appearance of the cytoplasm, which was almost entirely absent in the retroperitoneal tumor, in which many of the cells were plump and spindle shaped. The nuclei were fairly regular, with slight variations in staining characteristics but no evident mitoses. The early and late lesions of the skin were diagnosed as myoblastoma, as was the tumor found in the ovaries and the retroperitoneal mass.

COMMENT

All 4 cases were typical histologically of so-called granular cell myoblastoma. In the first 3 cases the tumor was nonencapsulated and locally invasive. In case 3 there was actual destruction of the neighboring tissue by the lingual neoplasm. In none of these cases were longitudinal or cross striations present, nor was there any definite pattern

EXPLANATION OF FIGURE.

Fig. 5 (case 4).—High power view of the tumor cells in the early lesion of the skin. × 550.

Fig. 6 (case 4).—A typical field from the tumor in the right ovary, which was identical in histologic appearance with the tumor in the left ovary. × 122.

Fig. 7 (case 4).—Section from the retroperitoneal mass showing a tendency of the cells to be more spindle shaped. The cytoplasm is finely granular. × 550.

Fig. 8 (case 4).—Microscopic appearance of the tumor which was removed from the perineum a year after the pelvic operation. × 550.

to the arrangement of the cytoplasmic granules. Sections of the myoblastoma of the tongue failed to show any forms transitional from myoblastoma cells to striated muscle. However, there was a remarkable organoid or pseudoalveolar pattern to the arrangement of the myoblastoma cells which gave this tumor a strong resemblance to neoplasms arising from endocrine glands.

A new factor entered into the fourth case which was not present in the others, namely, the presence of metastatic nodules. If one can judge the age of a tumor by size, the primary growth should have been either the ovarian or the retroperitoneal. However, from the standpoint of the known age of a lesion, the fact that the axillary subcutaneous nodule had been present for ten years or more would suggest that this was the original lesion. Although it is unusual for tumors of the skin to metastasize in such a manner, the behavior of slow-growing malignant melanoma of the skin offers a counterpart to this particular picture.

SUMMARY

The third of the 4 cases of granular cell myoblastoma reported is unusual because the tumor caused the death of the patient through local invasion and erosion of a large vessel.

The fourth case is unusual because of the widespread subcutaneous tumors and the involvement of both ovaries. It is believed to be the first case of granular cell myoblastoma reported in which the ovaries were involved.

Cases 3 and 4 are included in this paper with the permission of Dr. Violet Keiller, pathologist of Hermann Hospital, Houston, Texas.

TOXICOLOGY OF 1,2-DICHLOROPROPANE (PROPYLENE DICHLORIDE)

III. Pathologic Changes Produced by a Short Series of Daily Exposures

BENJAMIN HIGHMAN, M.D.
AND
LEON A. HEPPEL, M.D.
BETHESDA, MD.

THE COMPOUND 1,2-dichloropropane, $CH_2Cl.CHCl.CH_3$, is a colorless liquid with a characteristic and rather unpleasant odor. It has a specific gravity of 1.1593 at 20/20 C. and a boiling point of 96.8 C. It is finding extensive use as a solvent and as an insecticide. A mixture of dichloropropane and dichloropropylene in various proportions is applied to the soil for killing nematodes on the roots of pineapple plants and a wide variety of truck crops. Dermatitis has occurred among workers using this mixture as a soil fumigant.

In 1932 Wright and Schaffer [1] described the pathologic changes occurring in dogs after oral administration of dichloropropane to test its anthelminthic properties. However, as far as could be determined, no pathologic or toxicologic studies of the effects of inhalation of this compound are recorded in the literature other than the first two papers of this series.[2] Because our previous experiments were devised to permit study of the effects of a long-continued series of daily inhalation exposures, only a small number of animals that died or were killed after a few exposures to dichloropropane were studied histologically. In general, it was found that such animals showed far greater pathologic changes than those killed after surviving many exposures.

Accordingly, the following experiments were devised to permit more adequate study of the character, the development and the frequency of any early lesions caused by inhalation of 1,2-dichloropropane. Experiment A was devised to permit study of the pathologic changes occurring during a short series of daily exposures, and experiment B, to permit study of the changes following a single seven-hour exposure, to 2,200 parts per million (p.p.m.) of dichloropropane for comparison.

From the Pathology Laboratory and the Industrial Hygiene Research Laboratory, National Institute of Health, United States Public Health Service.

1. Wright, J. H., and Schaffer, J. M.: Am. J. Hyg. **16**:325, 1932.

2. (*a*) Heppel, L. A.; Neal, P. A.; Highman, B., and Porterfield, V. T.: J. Indust. Hyg. & Toxicol. **28**:1, 1946. (*b*) Heppel, L. A.; Highman, B., and Porterfield, V. T.: J. Pharmacol. & Exper. Therap. **87**:11, 1946.

In experiment A 30 young adult guinea pigs from our stock colony and 36 adult rats of the Sprague Dawley strain were exposed in the manner described in the preceding papers [2] to 2,200 p.p.m. of 1,2-dichloropropane. Six additional guinea pigs and 6 rats of the same strain and approximately the same age and weight as the exposed animals were used as controls. These were kept in cages adjoining the experimental animals, were fed the same stock diet, previously described,[2a] and were handled similarly except that they were not placed in the exposure chamber. Three guinea pigs were killed sixteen hours after the end of a seven hour exposure to 2,200 p.p.m. of dichloropropane. The others were killed immediately after the last exposure as follows:

3 guinea pigs and 3 rats after one four hour exposure
3 guinea pigs and 3 rats after one seven hour exposure
5 guinea pigs and 6 rats after two seven hour exposures
5 guinea pigs and 5 rats after three seven hour exposures
4 guinea pigs and 5 rats after four seven hour exposures
5 rats after five seven hour exposures

One guinea pig died during and 3 several hours after the second exposure, and 2 died during and 1 after the third exposure. Six rats died several hours after one seven hour exposure, and 2 died during and 1 after the second exposure. The animals that died were not studied histologically.

In experiment B (single exposure) 33 young guinea pigs from our stock colony, each weighing 600 to 800 Gm., and 33 adult rats of the Sprague Dawley strain, each weighing 150 to 200 Gm., were given one seven hour inhalation exposure to 2,200 p.p.m. of 1,2-dichloropropane. In addition, 3 unexposed guinea pigs and 3 rats served as controls. The exposed animals were killed at intervals after the single exposure as tabulated.

	Animals Killed After Given Number of Days										Animals That Died	Total	Controls
	0	1	2	4	7	9	11	14	16	21			
Guinea pigs.....	3	5	5	3	5	3	2	2	2	3	..	33	3
Rats.....	3	5	5	3	5	5	..	5	..	..	2	33	3

Two rats that died shortly after the exposure were not studied histologically because of advanced autolysis.

Autopsies were performed on all the experimental animals immediately after they were killed. Many animals showed gross evidence of slight visceral congestion and a fatty liver, and cut sections of the adrenal glands of the guinea pigs often showed a dark hemorrhagic central portion. Tissues were fixed immediately in Orth's solution, and routine sections of the organs were stained with azure eosinate [2a] and with iron hematoxylin and Van Gieson's solution of trinitrophenol, U. S. P. (picric acid) and acid fuchsin. Paraffin sections of liver and spleen were examined for hemosiderin.[3] Frozen sections of heart, liver and kidney were stained for fat by the method of Lillie and Ashburn.[4]

MICROSCOPIC CHANGES IN GUINEA PIGS

Certain lesions were seen in some of the guinea pigs used as controls, but such lesions were generally more extensive and severe in the exposed animals. These lesions included interstitial and lobular pneumonia, splenic suppuration and necrosis, and occasional small hepatic foci of coagulation necrosis, often marginated by monocytes.

2a. Lillie, R. D.: J. Tech. Methods **24**:43, 1944.
3. Highman, B.: Arch. Path. **33**:937, 1942.
4. Lillie, R. D., and Ashburn, L. L.: Arch. Path. **36**:432, 1943.

The specific lesions, found only in exposed guinea pigs, were fatty degeneration of the liver and the kidneys and necrosis of the adrenal glands. In general, the fat in the liver was irregularly distributed as fine to moderately coarse intracellular globules throughout the parenchyma. The fat in the kidney occurred as fine globules confined chiefly to the basal portion of the epithelium of the convoluted tubules and thick portions of the loops of Henle. The amount of fat seen in microscopic sections of the liver and the kidney in experiment A (repeated exposures) was small to moderate in animals killed after one and two seven hour exposures to 2,200 p.p.m. of 1,2-dichloropropane, large after three daily exposures and minimal in those killed after four exposures. In experiment B 1 of the 3 animals killed immediately after the single exposure showed a moderate and 1 a small amount of fat in the heart, the liver and the kidney. No significant amount of visceral fat was seen in any of the other animals in this experiment. Sections of liver of a limited number of animals in experiment B were prepared and stained for glycogen. Most animals had a marked decrease of glycogen in the liver immediately and twenty-four hours after the single exposure, a normal amount two days and a very large amount four days or more after the exposure. In paraffin sections of these glycogen-laden livers, most of the liver cells, particularly the centrolobular ones, appeared swollen, with pale, vacuolated cytoplasm.

Lesions in the adrenal cortex occurred in all exposed guinea pigs and varied in severity with the individual animal, the time elapsed since exposure and the number of exposures.

In guinea pigs killed immediately after single four hour and seven hour exposures, the inner portion of the adrenal cortex presented slight to moderate cytoplasmic oxyphilia and nuclear pyknosis, slight to marked congestion and structural disorganization and frequently one or more small areas of hemorrhage grading into hemorrhagic necrosis. In experiment A 1 animal killed after a single seven hour exposure showed diffuse hemorrhagic necrosis of the zona reticularis grading peripherally into a broad zone of congestion and hyaline and karyorrhectic necrosis.

The adrenal glands of guinea pigs killed sixteen, twenty-four and forty-eight hours after the end of a single exposure and immediately after two daily exposures presented a usually fairly well delineated area of cortical coagulation necrosis which involved all but a narrow outer rim of the cortex. In this necrotic area there was some distortion of structure with a variable amount of intercellular fibrinoid exudate. The cytoplasm of the necrotic parenchymal cells was deeply eosinophilic and sometimes vacuolated, and their nuclei were poorly stained and less often pyknotic, fragmented or apparently absent. The endothelial cells showed similar changes. Along the congested border of the necrotic area were occasional mononuclear cells and many neutrophils and fragmented nuclei, often forming a continuous or interrupted thin layer. Between this and the viable cortex and medulla was a narrow congested zone, which often showed some scattered neutrophils and, particularly around the medulla, sometimes graded into hemorrhagic necrosis.

Guinea pigs killed after three and four exposures showed similar cortical changes, but usually the viable cortex was slightly thicker and the layers of neutrophils near the congested borders of the necrotic area were broader and further removed from the viable cortex and medulla. The central portion of the necrotic area showed extensive karyolysis and often included one or more foci marginated or infiltrated by neutrophils. The necrotic parenchymal cells in such foci were often hyalinized, poorly outlined or agglutinated.

In guinea pigs killed four and seven days after a single exposure the viable cortex was thicker than in more recently exposed animals. In the necrotic area

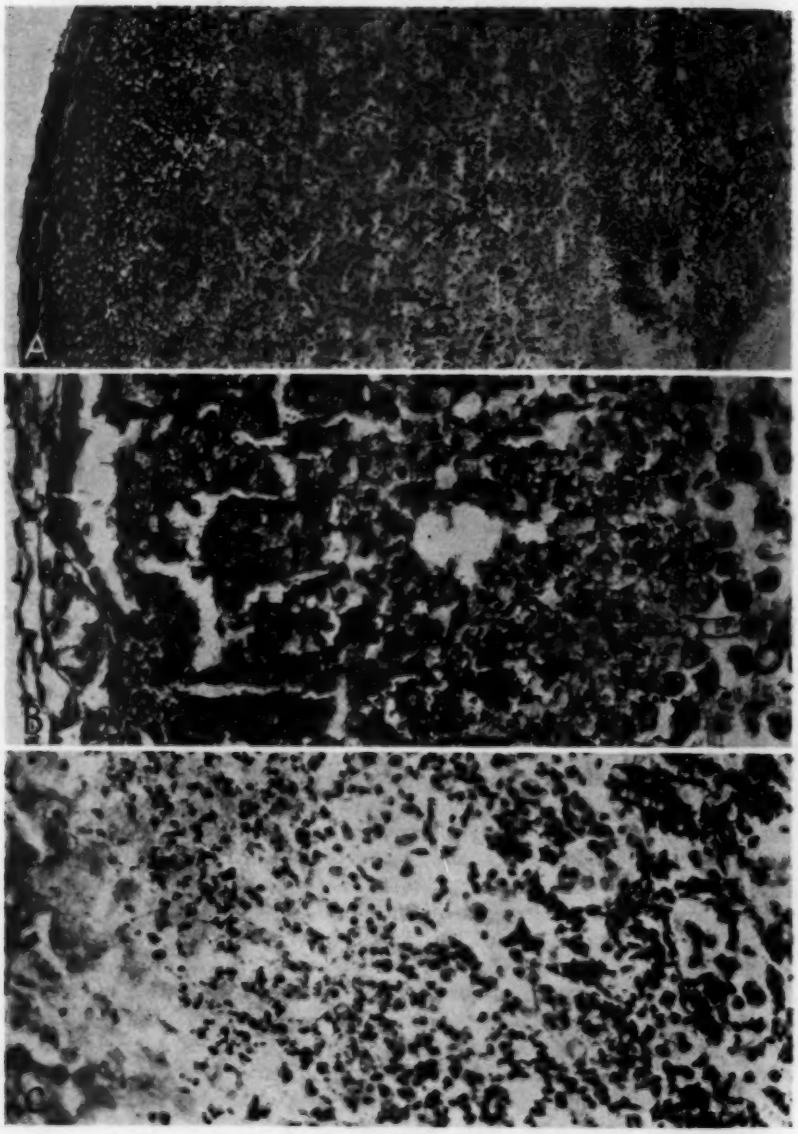

Fig. 1.—Photomicrographs of adrenal gland of a guinea pig killed immediately after two seven hour exposures to 2,200 p.p.m. of 1,2-dichloropropane. Azure eosinate stain.

A, large cortical area of necrosis marginated by leukocytes. Congested medulla is on the right. × 55.

B, viable cortex and congested leukocytic zone marginating the necrotic area on the right. × 250.

C, congested medulla and leukocytic zone marginating the necrotic area on the left. × 250.

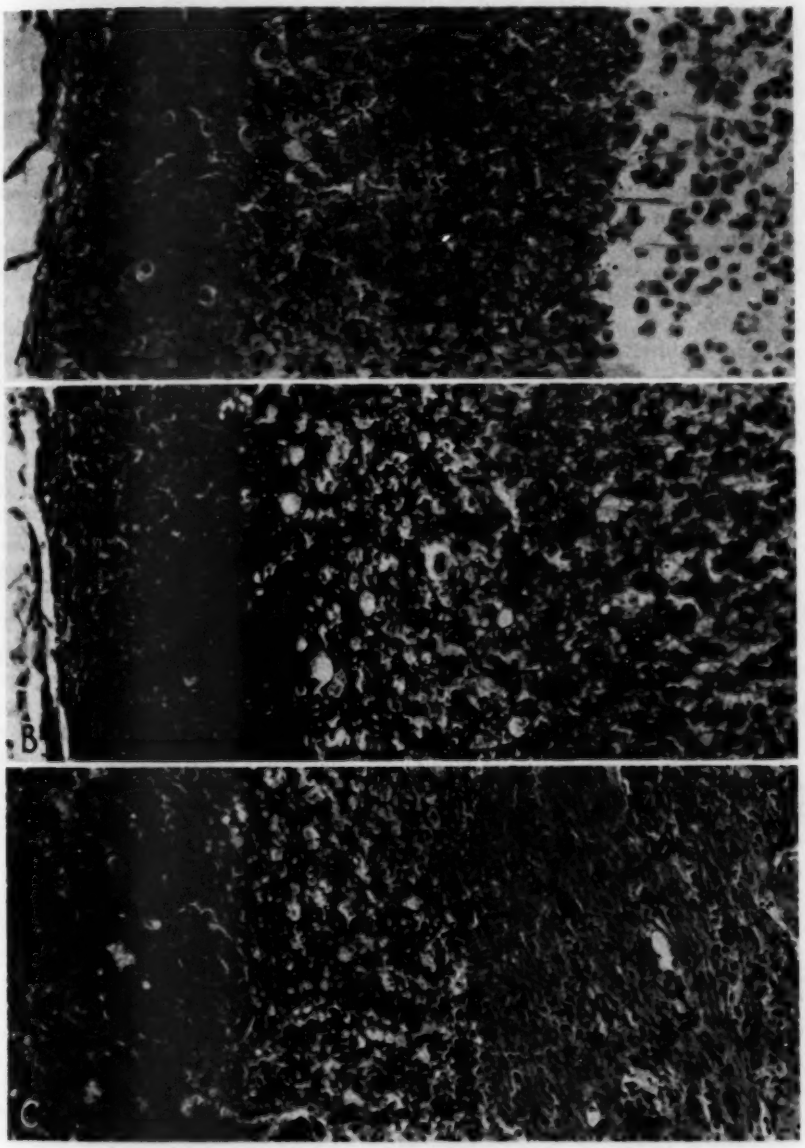

Fig. 2.—*A*, outer portion of adrenal cortex of a guinea pig killed twenty-four hours after a single seven hour exposure to 2,200 p.p.m. of 1,2-dichloropropane. Note mitotic figures in the viable cortex. Azure eosinate; × 150.

B, adrenal cortex of a guinea pig killed seven days after a single seven hour exposure to 1,2-dichloropropane. Note the layer of epithelioid cells bordering the necrotic area. Azure eosinate; × 150.

C, adrenal gland of a guinea pig killed eleven days after a single seven hour exposure to 1,2-dichloropropane. Note the layer of epithelioid cells contiguous with the connective tissue layer marginating the medulla on the right. Azure eosinate; × 150.

the central portion showed some scattered neutrophils and extensive hyalinization, karyolysis, cytolysis and vacuolation of the parenchyma. The submarginal layers of neutrophils were narrow, indistinct or absent. The congested border of the necrotic area adjoining the viable cortex was occupied by closely packed lipoid-laden large mononuclear cells of the epithelioid type (described more fully later) forming a layer ranging up to 200 microns in diameter. These epithelioid cells were often separated into columns by radiating slender septal downgrowths of swollen endothelium and fusiform fibroblasts. The congested border of the necrotic area adjoining the medulla often showed extensive extravasation of red blood cells and, in some animals, slight to marked proliferation of fusiform fibroblasts grading into a thin layer of fibroblastic connective tissue encircling the medulla. Many of these fusiform cells were laden with lipoid material, and, in some animals, with pigment giving the prussian blue reaction for iron (hemosiderin). In one adrenal gland the connective tissue layer was focally contiguous with the layer of epithelioid cells.

Guinea pigs killed nine, eleven, fourteen and sixteen days after one exposure showed progressive thickening of the adrenal cortex, extensive vacuolation and progressive reduction in size of the necrotic area, and gradual thinning of the layer of epithelioid cells, which often became continuous with the connective tissue layer as already described. Of 3 killed twenty-one days after a single exposure, the layer of epithelioid cells was present in only 1, and the necrotic area had completely disappeared in all. The connective tissue layer about the medulla showed much fat and hemosiderin.

Mitotic figures occurred chiefly in the zona fasciculata, particularly near the necrotic border. They were absent or rarely seen in the cortex of any control animal or any exposed animal killed immediately or more than nine days after one exposure to dichloropropane. In single microscopic cross sections of the adrenal glands of individual animals, mitotic figures numbered 0 to 4, 2 to 29 and 3 to 36 in groups of guinea pigs killed immediately after two, three and four exposures, respectively. In experiment B they numbered from 3 to over 300 per microscopic section in guinea pigs killed one and two days after a single exposure, and 6 to 20, 0 to 10 and 0 to 2 in those killed four, seven and nine days, respectively, after the single exposure.

In line with previous observations,[5] our unexposed controls showed only a small amount of lipoid material in the zona glomerulosa and abundance of lipoid material occurring as fairly uniform fine droplets confined chiefly to the outer half of the zona fasciculata. Most guinea pigs killed immediately after two to four exposures and a lesser number of those killed sixteen hours to four days after a single exposure showed a slight to moderate increase of lipoid material in the zona glomerulosa. Except for the layer of cells bordering the necrotic area, the viable portion of the zona fasciculata often showed a slight decrease of lipoid material with a relative increase of the number of coarser globules. The necrotic area showed many coarse lipoid globules, and as the length of time after a single exposure or the total number of exposures increased there was generally a corresponding decrease in the amount of fat in the necrotic parenchymal cells and an increase of the amount in the infiltrating neutrophils and mononuclear cells.

In general, the epithelioid cells in the necrotic area were sharply delineated and readily distinguished from the adjacent regenerating cortical cells. The latter appeared fairly uniform in size and shape with a centrally placed large spherical nucleus and abundant, usually lightly eosinophilic cytoplasm filled with small lipoid

5. Jaffé, R.: Anatomie und Pathologie der Spontanerkrankungen der kleinen Laboratoriumstiere, Berlin, Julius Springer, 1931.

globules. In contrast, the epithelioid cells in many areas varied markedly in size and shape. Their nuclei were round, ovoid, elongate or irregular in shape, often eccentric and generally more deeply stained, with less eosinophilic karyoplasm, than those in the adjacent cortex. The cytoplasm of the epithelioid cells was poorly stained and contained few to many unevenly spaced lipoid globules of variable size and some nonlipoid vacuoles. Even when mitotic figures were numerous in the regenerating cortex, none were seen in the subjacent epithelioid cells.

The adrenal glands of guinea pigs killed immediately after a single seven hour exposure to 2,300 p.p.m. of dichloropropane showed slight to marked congestion and edema of the medulla. In animals killed after two to four daily exposures and sixteen to forty-eight hours after one exposure the medulla showed in addition extensive hemorrhagic extravasations, lymphocytic and neutrophilic infiltration and disorganization of the nests of chromaffin cells. The cytoplasm of these cells was often vacuolated, and their nuclei were occasionally pyknotic, poorly stained or fragmented. A few cells were necrotic, many were atrophic, and there appeared to be a slight to marked reduction in their numbers. Fine fat droplets were seen occasionally in some chromaffin cells as well as in isolated cortical cells in the medulla. The amount of chromaffin pigment was often reduced. An occasional mitotic figure was seen in the chromaffin cells of 1 guinea pig killed after three exposures and in 1 after four exposures.

Most animals killed four and seven days after exposure showed less extensive hemorrhage and some proliferation of fibroblasts and deposition of hemosiderin in the medulla. Most animals killed nine days or more after one exposure showed little or no hemorrhage, a restoration of normal structure and amount of parenchyma, a decrease of infiltrating cells and a slight increase of hemosiderin.

MICROSCOPIC CHANGES IN RATS

Specific lesions were found in the livers, the kidneys and the adrenal glands.

In experiment A (repeated exposures) no significant changes were seen in the livers of rats exposed for only four hours. One of 3 rats killed after one seven hour exposure showed slight, diffuse, fine droplet fatty degeneration of the liver. Five rats killed after two exposures showed marked diffuse fatty degeneration; 4 of them showed also extensive, often confluent centrolobular necrosis involving more than half the parenchyma. Some lobules showed little or no involvement, while others were largely or completely necrotic. In the necrotic areas, the liver cords were often narrowed, distorted or disorganized; the liver cells were poorly outlined, their cytoplasm was deeply eosinophil, with occasionally basophil stippling, and their nuclei were often inapparent, poorly stained, pyknotic or fragmented. Kupffer cells showed less definite changes. The sinusoids in the necrotic areas were often narrowed and distorted and contained variable numbers and proportions of red blood cells, neutrophils and pyknotic and fragmented nuclei and nuclear debris. There were also some lymphocytes and occasional larger polyhedral or stellate cells with deeply staining nuclei and a small amount of cytoplasm, often containing some fine lipoid globules. Some necrotic areas showed foci of hemorrhage, and many showed a narrow peripheral hemorrhagic zone.

One of the 5 rats killed after three exposures showed a more advanced similar necrosis and narrowing of the liver cell cords. Another showed subtotal replacement of the central third of the hepatic lobule by closely packed red blood cells and fat-laden mononuclear cells similar to those already described. Few Kupffer cells, lymphocytes and occasional necrotic liver cells remained, chiefly near the midzone. There was a moderately broad midzonal area of fatty degeneration bordering the necrotic area. The other 3 rats showed intermediate changes. Rats

killed after four exposures showed a narrow centrolobular cellular zone composed chiefly of monocytes with few or no evident necrotic cells and surrounded by a narrow zone of fatty degeneration. Rats killed after five exposures showed either no change or only a few centrolobular lymphoid cells and monocytes with a few marginal fat-laden liver cells. Numerous mitotic figures were seen only in 1 of 5 rats killed after three exposures.

In experiment B no significant changes were seen in the livers of rats killed immediately and seven days or more after the single seven hour exposure to 2,200 p.p.m. of 1,2-dichloropropane. The 5 rats killed twenty-four hours after the exposure showed moderate to marked, midzonal to diffuse, fine droplet fatty degeneration of the liver and centrolobular necrosis. The latter was similar to but more sharply demarcated and less extensive and less hemorrhagic than that observed in the rats killed immediately after the two exposures. The hepatic lesions in rats killed two and four days after the single exposure were essentially similar to those seen in rats killed immediately after four and five daily exposures, respectively. Only 3 of 5 rats killed two days and 1 of 3 killed four days after the single exposure to dichloropropane showed some necrotic liver cells in a few of the centrolobular lesions. Only the livers of rats killed two days after one exposure showed a few to moderately numerous scattered mitotic figures. Most rats killed one and two days after the single exposure showed marked depletion of glycogen in the liver. Most rats killed four days or more after the single exposure to dichloropropane showed hemosiderin in some Kupffer cells, chiefly centrolobularly.

In the kidney, fine droplets of fat occurred chiefly in the epithelium of many convoluted tubules and thick portions of the loops of Henle. In experiment A a small amount of renal fat was seen in 3 of 6 rats killed after two daily exposures, in 4 of 5 after three, in 1 of 5 after four and in none of 5 after five exposures. In experiment B a small amount of renal fat was seen only in 4 of 5 rats killed one day and 2 of 5 killed two days after a single exposure; a minimal amount was seen in the kidneys of 3 of 5 rats killed seven days after exposure.

The fat in the adrenal cortex was moderately reduced in rats killed at once after a four hour exposure to 2,200 p.p.m. of dichloropropane, was markedly reduced after one and two seven hour exposures, slightly reduced after three and within normal limits after four and five such exposures. In experiment B the amount of fat in the cortex was slightly to moderately reduced only in rats killed at once and twenty-four hours after a single exposure.

In experiment A hemosiderin in small amounts was seen in the spleen only in rats killed after five exposures and in 3 of 5 rats killed after four exposures. In experiment B hemosiderin was seen in both controls and exposed animals in variable amounts.

Other changes included slight bronchitis seen in 6 rats killed after three exposures; 1 of these showed in addition slight interstitial pneumonitis, and 1 showed a seromonocytic lobular pneumonia. In experiment B interstitial pneumonitis was seen in occasional animals in nearly all groups, including the controls.

COMMENT

As is well known, intermittently exposed laboratory animals may develop increased resistance to certain toxic substances quite rapidly.[6] It would appear that 1,2-dichloropropane is such a substance. Thus, clinically we have previously noted [2a] that the first few exposures to dichloropropane cause marked narcosis, whereas subsequent exposures have no

6. Eschenbrenner, A. B., and Miller, E.: J. Nat. Cancer Inst. **6**:325, 1946.

apparent narcotic effect on the animals. The present investigation shows that this increasing resistance is reflected also in the pathologic picture. Thus, when we compare the results in experiments A and B, we find in general that the lesions occurring during a series of daily exposures to dichloropropane are similar to those following a single exposure and that such lesions, though somewhat more severe and prolonged, apparently undergo rapid resolution despite continuation of daily exposures.

The rapidity of development and the apparent complete resolution of such lesions can be illustrated by giving a brief composite picture of the changes observed in the livers of exposed rats in experiment A. Thus, we found no significant hepatic changes immediately after one four-hour exposure to 2,200 p.p.m. of 1,2-dichloropropane, slight diffuse fatty degeneration after one seven-hour exposure, marked diffuse fatty degeneration and extensive, often confluent centrolobular coagulation and focal hemorrhagic necrosis after two such exposures, centrolobular congestion and cellular infiltration with occasional necrotic liver cells and midzonal fatty degeneration after three exposures, slight centrolobular lymphocytic and monocytic infiltration and midzonal fatty degeneration after four exposures and minimal or insignificant changes after five such exposures to dichloropropane. Similar rapid changes were seen in other organs.

In general, the results of the present experiment are in keeping with those reported in our first paper [2a] in a few similarly exposed animals. In the earlier experiments a few guinea pigs that died showed extensive centrolobular coagulation necrosis similar to that seen in the rats. Since the animals that died in earlier experiments often showed more severe lesions than similarly exposed killed animals, it seems not unlikely that dichloropropane can produce such extensive hepatic necrosis only in some of the more susceptible guinea pigs and that it may have produced some of the small hepatic foci of coagulation necrosis in the exposed guinea pigs in our present experiments, even though similar foci were seen occasionally in control animals.

In the earlier experiments, only occasional minimal lesions were noted in animals surviving many exposures to dichloropropane. In the light of the present experiments it seems probable that severe lesions were produced initially in many or all of these much exposed animals and that such lesions underwent early resolution despite further exposures, leaving little or no trace of their former presence. Thus, in our earlier experiments the adrenal glands of guinea pigs killed after surviving many exposures showed a subcortical layer of connective tissue. The observations in our present experiments suggest that this connective tissue layer may have replaced an earlier area of hemorrhagic necrosis at the border of the cortex and the medulla.

Lesions in the adrenal glands of guinea pigs somewhat similar to those rated in our experiments with dichloropropane have been reported

to follow the administration of carbon tetrachloride.[7] Phelps and Hu[8] reported that necrosis of the adrenal cortex following subcutaneous injection of carbon tetrachloride appeared later and disappeared earlier than the lesions in the liver. In contrast, our experiments show that dichloropropane can produce severe lesions in both the cortex and the medulla of the adrenal gland of the guinea pig before lesions in the liver become manifest. It seems not unlikely, therefore, that in the guinea pig the damage to the adrenal gland may be more important than that to the liver in accounting for the mortality and the toxicity of dichloropropane. In view of these results in guinea pigs, perhaps the depletion of lipoid material and other slight changes found at times in the adrenal glands of rats and other animals exposed to dichloropropane and some other compounds[9] should merit more attention from a toxicologic standpoint.

SUMMARY

Two experimental groups, each made up of guinea pigs and rats, were exposed to 2,200 p.p.m. of 1,2-dichloropropane. In one experiment the animals were killed for histologic study at intervals during a short series of daily exposures; in the other experiment they were killed at intervals following one seven-hour exposure.

Guinea pigs showed extensive coagulation and focal hemorrhagic necrosis of the adrenal cortex, congestion with hemorrhage and parenchymatous degeneration of the adrenal medulla, and fatty degeneration of the liver and the kidney. Rats showed hepatic centrolobular necrosis, fatty degeneration of the liver and the kidney, and depletion of the lipoid material of the adrenal cortex. In both experiments these lesions did not reach their full development generally until twenty-four to forty-eight hours after the end of the first exposure. These lesions were somewhat less severe and disappeared earlier in animals receiving one exposure than in those receiving daily exposures. However, except for the adrenal glands of guinea pigs, lesions were minimal or absent three or four days after the end of the first exposure even in the animals that continued to receive daily exposures. The necrotic area in the adrenal cortex did not disappear completely until two to three weeks after a single exposure.

These observations emphasize the importance of obtaining sufficient pathologic material early in a numerical series of intermittent exposures to toxic agents in order to determine the frequency, the character, the development and the resolution of any lesions produced.

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FIBRINOGEN PLASTICS

Tissue Reactions Induced by a Series of Fibrinogen Plastics Implanted in the Abdominal Wall of Guinea Pigs

ORVILLE T. BAILEY, M.D.
AND
RICHARD FORD, M.D.
BOSTON

THE NEW METHODS developed for the fractionation of human blood plasma have made it possible to prepare the constituent proteins in large amounts and in a high state of purity.[1] Several of the plasma proteins, notably fibrinogen, may be made into plastic materials.[2] The physical properties of these plastics vary greatly, depending on the plasticizer used as well as on the temperature and the pressure at which plasticization takes place. These properties have been described in detail elsewhere.[2]

In recent years a number of publications have appeared which deal directly or indirectly with the tissue reactions elicited by commercial plastics implanted in living tissue. Although many of these plastic materials have very different properties when the conditions of formation are altered, the investigations mentioned have largely been confined to unmodified commercial products. Since the fibrinogen plastics are easily made under controlled conditions in a research laboratory, it is worth while to study the tissue reactions induced by a series of modified plastics. In this way, it may be possible to characterize the

From the Departments of Physical Chemistry, Pathology and Legal Medicine, Harvard Medical School.

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The work described in this paper has been carried out in part under a grant from the Proctor Fund of Harvard University and in part under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

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2. Ferry, J. D., and Morrison, P. R.: J. Clin. Investigation **23**:566, 1944. Ferry, J. D., and Morrison, P. R.: Fibrin Film and Other Plastic Products from Human Plasma, to be published.

variations in tissue reactions to fibrinogen plastics due to several variables in composition. Furthermore, the study of this series may serve as a basis for comparison with studies of other groups of plastics used in medicine. This study was originally undertaken to determine whether or not fibrinogen plastics were suitable for use in surgical practice. The results, together with certain other material, were included in a report to the Proctor Fund, Sept. 1, 1942 ("The Behavior of a Series of Fibrinogen Plastics in Animal Tissues, with a Note on the Effect of Plasticizing Agents on Fibrinogen-Thrombin Films" by O. T. Bailey, R. Ford, and C.v.Z. Hawn).

METHODS FOR THE STUDY OF TISSUE REACTIONS TO FIBRINOGEN PLASTICS

A standard procedure was set up for the study of the series of fibrinogen plastics. The plastics to be tested were prepared under sterile conditions. Guinea pigs weighing 350 to 450 Gm. were used. The animal was anesthetized with ether and the abdomen shaved. A small incision was made in the abdominal skin and carried down to the deep fascia. A piece of plastic approximately 0.7 by 0.4 by 0.4 cm. was inserted into the fascial layer between the skin and the musculature; it was then pushed lateralward so that the plastic did not lie beneath the incision. The incision was then closed with one black silk suture. Aseptic technic was used for the operative procedure, but no dressing was applied. Four to six pieces, differing from one another in composition, were implanted in different portions of the abdominal wall of each animal. The animals were killed with chloroform at various intervals. The plastics and the tissues surrounding them were immediately removed and fixed in Zenker's fluid containing glacial acetic acid. After fixation, the tissues were embedded in paraffin, and sections were cut and stained by the eosin–methylene blue technic and occasionally by the hematoxylin–eosin method. The plastics tended to become tough in the graded alcohols used for dehydration of the tissue blocks. When this change was sufficient to preclude the cutting of satisfactory paraffin sections, the plastic was gently removed from the tissue block before embedding. The surrounding tissue was not adherent to the plastic until the plastic was almost completely absorbed.

EFFECT OF VARYING THE PLASTICIZER

A series of plastics was prepared with different plasticizers, other variables being kept constant. In each instance, the substrate was bovine fibrinogen, the pressure 120 pounds per square inch (8.5 Kg. per square centimeter), the temperature 100 C. and the length of time in the hot press thirty minutes. Equal parts of plasticizer and bovine fibrinogen were used (except in the tenth instance in the following list).

The plasticizers used were:

1. Glycerin
2. Glycerin plus 5 per cent thiocyanate
3. Ethylene glycol
4. Ethylene glycol plus 5 per cent sodium thiocyanate
5. Propylene glycol
6. Ethylene glycol monoacetate
7. Tetraethylene glycol
8. Water
9. Water plus 5 per cent sodium thiocyanate
10. No plasticizer.

The cellular responses to these plastics and to the plastics described in other sections of this report showed such great qualitative similarity that a single

description will suffice. The physical characteristics of the materials, their persistence in the tissues and the quantitative tissue reactions varied considerably and will be indicated for each of the plastics tested.

The initial cellular response consisted of slight cellular infiltration—polymorphonuclear leukocytes, followed by mononuclear cells and lymphocytes. The number of all these cells gradually increased somewhat; at the same time there was slight proliferation of fibroblasts with laying down of collagen. A few giant cells were formed along the edge of some of the plastics, but giant cells at this stage appeared in surprisingly small numbers or not at all. It was difficult to determine how much of the initial cellular reaction resulted from the trauma of inserting the plastic and how much from the irritation caused by the presence of the

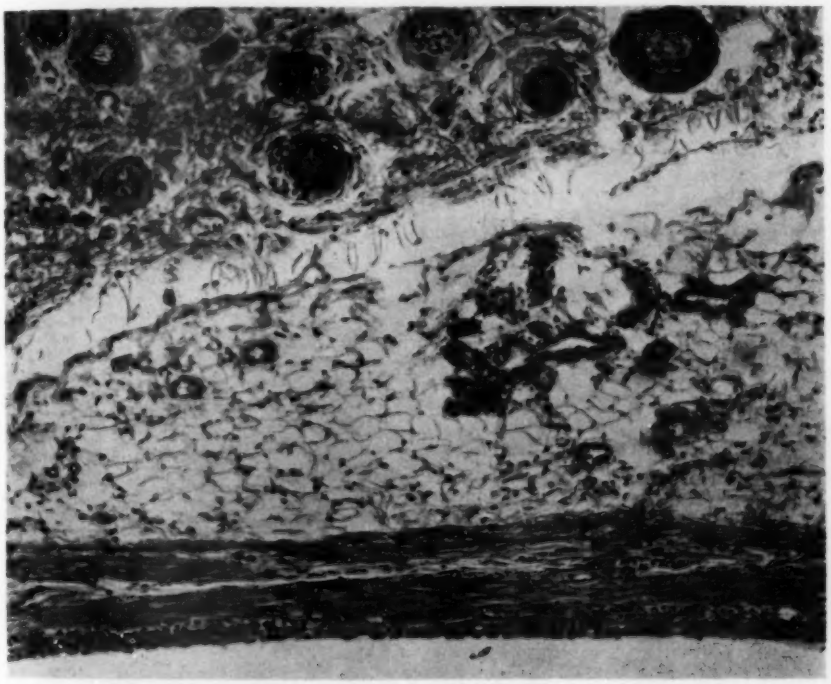

Fig. 1.—Tissue reaction to plastic made from bovine fibrinogen with glycerin as plasticizer (each 50 per cent) at 100 C. for two hours. Animal killed eight weeks after implantation. Hematoxylin-eosin stain; low magnification; plastic removed. The tissue closest to the plastic is at the lower margin of the photomicrograph.

implant. The giant cells were almost certainly the result of the presence of the plastic, while some of the polymorphonuclear leukocytes and mononuclear cells might well have appeared in response to the trauma.

Regardless of plasticizer, the plastics stained blue with eosin–methylene blue technic but took the eosin stain when the hematoxylin–eosin method was used. In the eosin–methylene blue sections they soon became eosinophilic along the line of contact with living tissue. As absorption progressed, the portion of plastic in contact with living tissue remained more eosinophilic than that at a distance

from living tissue. This staining change was accompanied by infiltration of many mononuclear cells, which contained eosinophilic material histologically identical with the surrounding plastic and judged to be phagocytosed bits of the material. Polymorphonuclear neutrophils made their appearance in the region of disintegration of the plastic. The mononuclear cells containing eosinophilic material became scattered through the connective tissue about the plastic as though they were moving away from the zone of phagocytosis. Scattered eosinophils and mononuclear cells were also found in this connective tissue. Small pieces were broken off at the edge of the plastic; these became surrounded by mononuclear cells and polymorphonuclear neutrophils. About some of them, giant cells were formed; even at this stage, however, giant cells were not a dominant

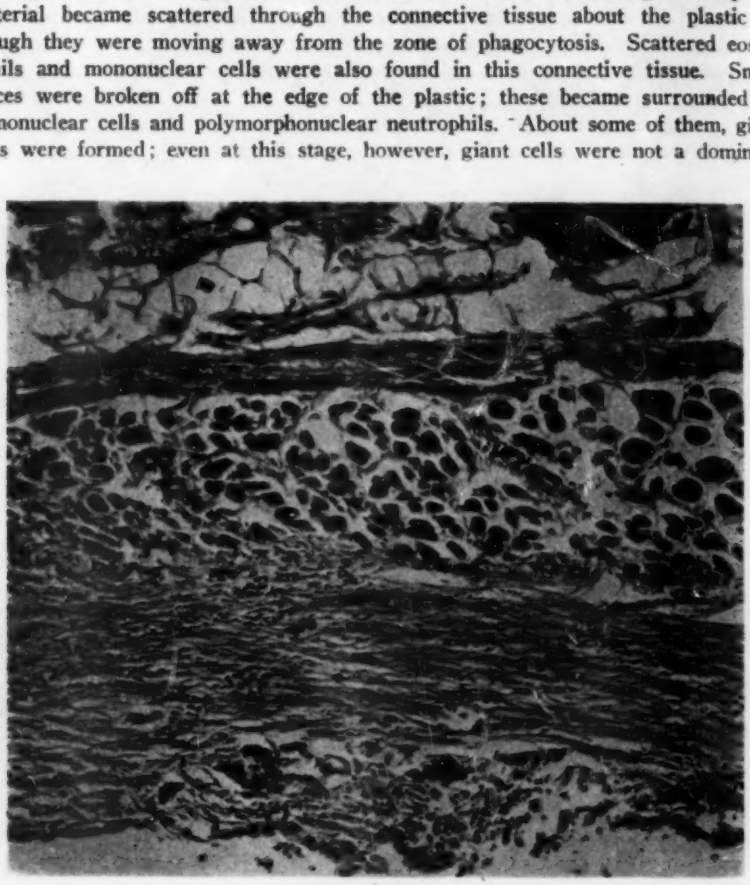

Fig. 2.—Tissue reaction to plastic made from bovine fibrinogen with water as plasticizer (each 50 per cent) at 100 C. for thirty minutes. Animal killed four weeks after implantation. Hematoxylin-eosin stain; low magnification; plastic removed. The tissue closest to the plastic is at the lower margin of the photomicrograph.

feature of the cellular response. The next step in disintegration was indicated in microscopic sections by the appearance within the plastic of a few widely separated strands of connective tissue, accompanied by small numbers of mononuclear cells and polymorphonuclear neutrophils. These strands extended all the way through the plastic at various angles. The mechanism concerned in their abrupt appearance was not determined from the microscopic sections. Complete disintegration of the plastic soon followed. During this process the polymorphonuclear neutrophils and mononuclear cells increased in number. While there

was active phagocytosis, there did not seem to be sufficient to account for the removal of all or even the larger part by this process alone. While there is no direct evidence, it seems probable that enzymatic activity played a large part in the disappearance of the material. The rapid completion of removal was judged to be due to the fact that living cells and tissue fluids had free access to all parts of the plastic after the ingrowth of the widely separated strands of tissue. The end result was a small fibrous cicatrix, identified with difficulty and often not found even when sections were cut from serial blocks of the entire region.

In spite of the qualitative similarity of the tissue reactions to plastics made with different plasticizers, there was considerable quantitative variation in the responses. The least reaction was obtained when ethylene glycol was the plasticizer. Plastics made with glycerin gave little more (fig. 1). Those made with water gave considerably more reaction (fig. 2) (there was one exception to this in the

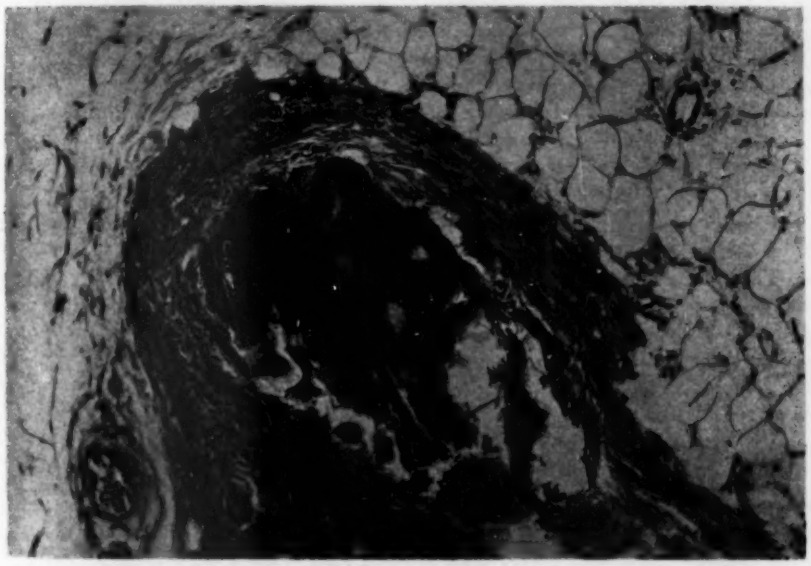

Fig. 3.—Tissue reaction to plastic made with ethylene glycol twenty-five weeks after implantation. Hematoxylin-eosin stain; low magnification.

series). The other specimens produced reactions which were intermediate between those produced by ethylene glycol plastics and those produced by water plastics. The plastic made of fibrinogen without plasticizer produced about the same reaction as the intermediate group of plastics. The addition of sodium thiocyanate had a variable effect on the amount of tissue reaction. In some cases the amount of reaction was unchanged, while in others it was increased. In no instance was the reaction diminished by the addition of sodium thiocyanate.

The glycerin plastics disappeared in six weeks to three months. The propylene glycol and ethylene glycol plastics survived in the tissues, being present in animals examined as long as six months after implantation (fig. 3). Plastics made with water disintegrated at about the same rate as those made with glycerin. The others occupied an intermediate position. The addition of sodium thiocyanate had no significant effect on the rate of disintegration of the materials.

EFFECT OF VARYING THE CONCENTRATION OF PROTEIN IN THE PLASTIC

A series of plastics was prepared with varying concentrations of bovine fibrinogen. All were heated at 100 C. at a pressure of 120 pounds per square inch for thirty minutes. The following variables were used in preparing the series of plastics:

1. Water 33 per cent—fibrinogen 67 per cent (tough, rubbery)
2. Water 67 per cent—fibrinogen 33 per cent (opaque, soft)
3. Water 80 per cent—fibrinogen 20 per cent (soft)
4. Water 91 per cent—fibrinogen 9 per cent (separated into clot and aqueous phases)
5. Ethylene glycol 33 per cent—fibrinogen 67 per cent (tough, rubbery)
6. Ethylene glycol 67 per cent—fibrinogen 33 per cent (soft)
7. Ethylene glycol 80 per cent—fibrinogen 20 per cent (weak, slightly opaque)
8. Glycerin 33 per cent—fibrinogen 67 per cent (tough, rubbery)
9. Glycerin 67 per cent—fibrinogen 33 per cent (soft)
10. Glycerin 80 per cent—fibrinogen 20 per cent (slightly opaque, weak)
11. Glycerin 10 per cent plus sodium thiocyanate 80 per cent—fibrinogen 20 per cent (clear, weak)
12. Glycerin plus 10 per cent sodium thiocyanate 91 per cent—fibrinogen 9 per cent (clear, very soft)
13. No plasticizer—fibrinogen 100 per cent (stiff, brittle)

Plastics containing 50 per cent plasticizer and 50 per cent protein were available from the previous series of experiments.

The difference in concentration of the protein had no effect on the character of the cellular response. Plastics containing 80 and 91 per cent water underwent almost complete disintegration in the tissues within three weeks. In other instances the persistence of the plastic was affected little by the change in concentration of the protein in spite of the alterations in physical properties due to the variations in composition.

EFFECT OF VARYING THE TIME OF HEATING

A series of plastics was prepared to test the effect of varying the length of the period during which the material was heated at 100 C. under 120 pounds' pressure per square inch. Equal parts of bovine fibrinogen and plasticizer were used in each instance. The plasticizers used and the periods of heating were as follows:

1. Water	5 min.
2. Water	15 min.
3. Water	30 min.
4. Water	120 min.
5. Glycerin	5 min.
6. Glycerin	15 min.
7. Glycerin	30 min.
8. Glycerin	120 min.

As the time of heating was lengthened, the plastics became darker brown, firmer and less flexible. No significant differences in tissue reaction to the plastics made with water resulted from the variation in the time of heating. In the case of the glycerin plastics the reaction was considerably greater at five minutes and at one hundred and twenty minutes than it was at fifteen minutes or thirty minutes. From these experiments we were unable to draw any general conclusions on the relation of the tissue reaction to the length of time the material was heated.

EFFECT OF VARYING THE PROTEIN USED AS SUBSTRATE

Each of the substrates used was mixed with an equal amount of water. The mixture was heated at 100 C. under a pressure of 120 pounds per square inch for thirty minutes. The substrates tested were:

1. Bovine albumin
2. Horse fibrin (Horse Fiber Powder)
3. Human fibrinogen
4. Casein
5. Bovine fibrinogen

The plastic made with bovine albumin produced a minimal tissue reaction, comparable to that produced by plastics composed of ethylene glycol and fibrinogen. When horse fibrin was used as the substrate, a severe tissue reaction was elicited, more extensive than that to any other plastic tested in the entire study. The commercial horse fibrin contained a much higher percentage of impurities than the bovine fibrinogen, which may account for some of the severity of the tissue reaction. Plastics with human fibrinogen and casein as substrates produced reactions similar to those appearing in response to plastics with bovine fibrinogen as substrate, described in previous sections of this report. No experiments with plastics made from homologous fibrinogen were carried out on animals.

COMMENT

The purpose in undertaking this study was to determine which of the plastics was most suitable for clinical trial. As experience with the fractionation of human and bovine plasma increased, Ferry and Morrison [2] and Bering [3] were able to produce from fibrinogen and thrombin other materials which suited the immediate problems of the armed forces better than did the plastics. These received clinical trial and were used in large amounts in the armed forces.[4] There may still be uses for the fibrinogen plastics in human surgery, as indicated by Blaine.[5] Should one of these plastics be required for human patients, the data recorded in this paper could be used in the selection of one with a suitable time of persistence and character of tissue reaction. The plastics tend to soften in the tissues long before they are completely absorbed.

In a series of experiments not recorded in detail, plastics were prepared with mixed plasticizers (e. g., fibrinogen 50 per cent, ethylene glycol 25 per cent, water 25 per cent). These gave tissue reactions resembling those in response to plastics made with the more reactive single plasticizer (in the example cited, a water-fibrinogen plastic). When any of these plastics is sterilized in steam, a considerable amount of the plasticizer is replaced by water, and the tissue reaction should be expected to be altered somewhat.

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When various plastic materials, e.g. nylon (a concentration product of hexamethylene diamine and adipsic acid) and lucite (methyl methacrylate), have been used in surgical practice, the investigators have usually been content to employ the unmodified commercial product. By trying a series of related plastics, as has been done for the fibrinogen plastics, one or several might be found especially suited for particular surgical needs.

SUMMARY

A series of plastics was prepared from various purified blood proteins, especially fibrinogen. Their physical properties could be varied over a wide range by altering the substrate, the plasticizer and the conditions of plasticization.

Studies were made to determine the tissue reactions elicited by a group of these plastics in the abdominal wall of guinea pigs. On the whole, the tissue reactions were relatively slight. The tissue reactions were affected by the nature of the substrate and of the plasticizer; they were much less affected by the concentration of the substrate and by the time of heating.

Case Reports

PRIMARY BRONCHIOGENIC LEIOMYOSARCOMA

MAJOR W. SPEARS RANDALL
AND
COLONEL BRIAN BLADES
MEDICAL CORPS, ARMY OF THE UNITED STATES

MESENCHYMAL tumors of bronchial origin are extremely rare. The most frequently reported of this group of mesenchymal lesions are the chondromatous tumors. Of tumors arising from smooth muscle and limited to the bronchus, 6 have been previously recorded.

Franco [1] reported the incidental finding of a tumor arising from the right upper lobe bronchus in a 56 year old woman who died of meningitis. The tumor was ovoid and circumscribed, measuring 13 by 11 by 9 cm., and histologically was a leiomyoma. In his report he cited 2 previous cases, one recorded by Forkel [2] and the other by Deussing.[3] In each of these 2 cases the tumor was found at autopsy; in Forkel's case it was solitary, while in Deussing's case it occurred as multiple bilateral pulmonary lesions, which suggested to some reviewers metastasis from similar tumors found in the patient's uterus.

Neumann [4] described a cancerous tumor of smooth muscle arising in the left upper lobe bronchus of a 66 year old woman, which metastasized throughout each lung and to the thyroid gland, the liver, the pancreas, the adrenal glands and the lumbar vertebrae.

Kramer [5] reported a case: A 15 year old girl complained of cough with recurrent blood-streaked sputum and clubbing of the fingers. Roentgen examination revealed a triangular shadow in the mesial portion of the lower lobe of the right lung. Bronchoscopy revealed partial occlusion of the bronchus of this lobe by a broad-based pedunculated tumor, diagnosed histologically as myoblastoma.

Brahdy [6] reported still another case: An 18 year old nurse, while under observation for early pulmonary tuberculosis, was found by roentgen examination to have a circumscribed tumor in the lower two thirds of the lower lobe of the right lung. This was successfully removed and a diagnosis of fibroleiomyoma made on microscopic examination.

From the Pathology Section of the Laboratory Service and the Thoracic Surgery Section of the Surgical Service, Walter Reed General Hospital, Washington, D. C., and the Department of Surgery, George Washington School of Medicine, Washington, D. C.

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3. Deussing, R.: Multiple primäre Myome der Lunge, Inaug. Dissert., Munich, R. Müller & Steinicke, 1912.

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The tumor reported here is the seventh of such mesenchymal tumors recorded in the literature.

REPORT OF A CASE

A well nourished Negro man aged 34 was admitted to Walter Reed General Hospital in August 1945 with chronic cough, dyspnea and weakness. The persistent cough began in the early part of 1943; however, hospitalization was not necessary during that period, and no roentgen examination of the chest was made. In November 1944, while at a high altitude overseas, the patient had hemoptysis of about 2 ounces (59 cc.). In February 1945 he was admitted to a hospital, at which time the cough was productive of thick, greenish yellow sputum and a diagnosis of "pneumonia, right lung," was made. There was persistent leukocytosis, and the sedimentation rate was 28 mm. in one hour. Roentgen examination of the chest revealed an area of density in the right hilar region, with a shift of the heart and the mediastinum to the right and an elevation of the right leaf of the diaphragm.

The patient was transferred to the Zone of the Interior, and in June 1945 there was roentgen evidence of appreciable enlargement of the bronchial neoplasm. Bronchoscopy at this time revealed a smooth, rounded tumor almost completely occluding the right main bronchus and partially covering the coryna. Repeated bronchoscopic resections of the tumor resulted in transient reexpansion of the right lung, with the mediastinum shifting back to a more normal position. The tumor during theses periods was visualized as a well circumscribed mass in the right main and right upper lobe bronchi.

As irradiation therapy was thought advisable, the patient was transferred to Walter Reed General Hospital with a diagnosis of bronchiogenic neoplasm, type undetermined. During bronchoscopy at this hospital considerable bleeding was encountered, this being controlled by sponges saturated with solution of epinephrine hydrochloride. A biopsy specimen was taken at this time and a diagnosis of low grade leiomyosarcoma made (fig. 1 *B*).

During this hospitalization the patient had hemoptysis on several occasions, varying in amounts up to 400 cc. Because of the location and the type of the tumor, with involvement of the coryna and repeated episodes of hemoptysis, pneumonectomy was considered the only possible method of prolonging the patient's life. This was attempted on October 15. As the right main bronchus was being exposed, the portion of the tumor at the coryna became detached so that it completely obstructed the air passages; this obstruction was relieved by immediate bronchoscopy. It was decided to complete the operation in a second stage at a later date. However, during closure of the chest there was profuse bleeding into the left main bronchus and all efforts of resuscitation were of no avail.

Postmortem Examination.—Externally the body revealed no abnormalities except for the wound left by the recent thoracotomy with resection of the right fifth rib. The right pleural cavity contained approximately 100 cc. of fresh blood and no adhesions. The left pleural cavity was free of fluid and adhesions, while the lung was partially collapsed. The peritoneal cavity contained a normal amount of clear, thin fluid. The abdominal viscera were in their normal position and revealed no abnormalities.

The lungs, the trachea and the larynx were removed en masse. The right lung was dark purple and the surface smooth and glistening. A circumscribed mass was palpable in the right hilar region, extending into the upper lobe of the lung. The trachea and bronchi were opened posteriorly, revealing a friable mass 2 cm.

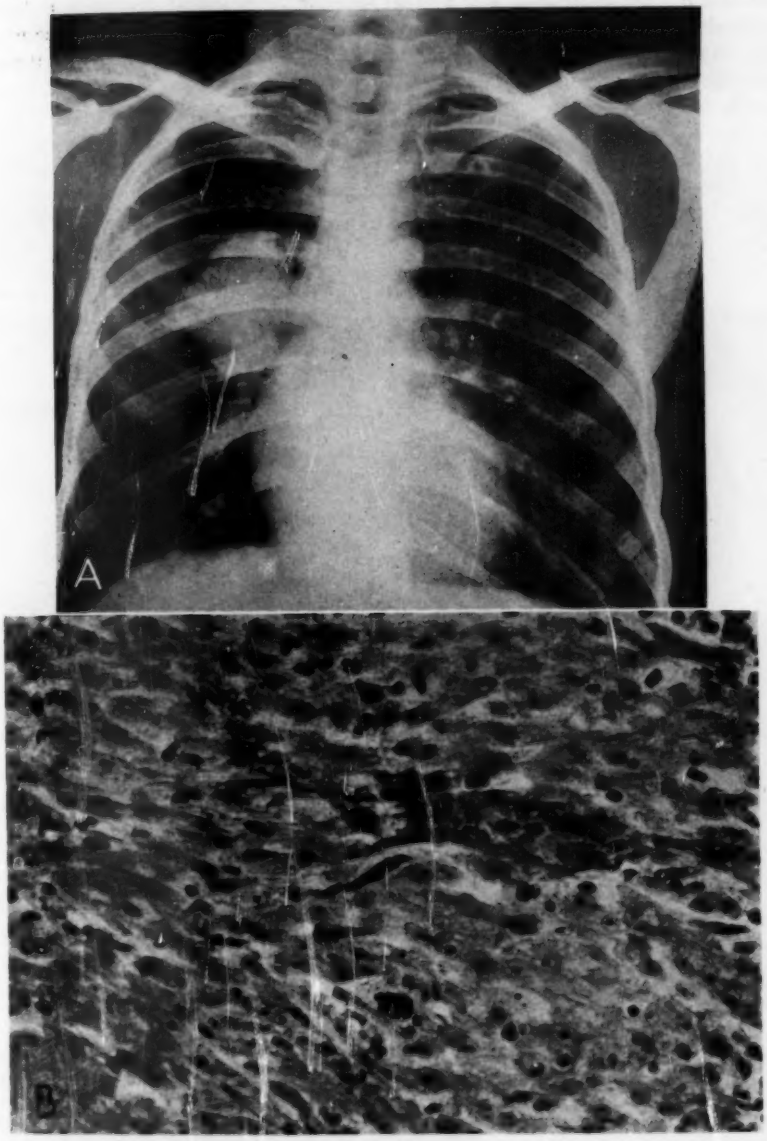

Fig. 1.—*A*, roentgenogram taken in August 1945 after bronchoscopic resection of the tumor attached to the coryna. It shows the lung almost completely expanded. The neoplasm appears essentially the same as when visualized two months previously.

B, photomicrograph of a section of the bronchoscopic biopsy specimen. Note the complete absence of epithelial structures, the fragment being composed of compact ovoid and spindle-shaped smooth muscle cells. × 400 (United States Army Medical Museum Neg. 94799).

in diameter, attached to the coryna by a pedicle approximately 3 mm. in thickness and length. Detached from this portion was the large friable hemorrhagic tumor enclosed within the right main bronchus proximally, but extending along the upper lobe bronchus, where the adjacent lung parenchyma was infiltrated. The left main bronchus was completely filled with fresh blood and clots.

Fig. 2.—Upper and middle lobes of the lung containing the tumor sectioned after fixation. The tonguelike projection represents the middle lobe, entirely free from tumor. Note the sharp line of demarcation between the tumor and the surrounding hemorrhagic lung parenchyma.

When the lung was sectioned, the tumor was found to be irregularly circumscribed, 10 to 14 cm. in diameter, soft, yellowish to hemorrhagic and limited to the upper lobe. The surrounding parenchyma was atelectatic and hemorrhagic (fig. 2).

The heart and the abdominal viscera were removed, and careful gross and microscopic examination revealed no evidence of tumor or other significant abnormality.

Microscopic Examination.—Sections of the tumor removed at autopsy presented the typical appearance of an extremely cellular but locally infiltrative leiomyosarcoma. The tumor was composed of cells of a single type, varying from ovoid to extremely elongated forms compactly arranged in a fasciculated pattern. Irregularly throughout the tumor were broad bands of collagenic tissue, in some parts forming septums. The centrally located nuclei seen when the neoplastic cells were cut longitudinally were ovoid, generally vesicular, with small but prominent nucleoli. An occasional mitotic figure was noted, also multinucleated forms (fig. 3).

In addition to hematoxylin-eosin preparations, sections treated with Van Gieson's connective tissue and Masson's trichrome stains were studied. With Van Gieson's method the cytoplasm of the neoplastic cells appeared yellow, while with Masson's trichrome stain the cells were of a dusty brick red color.

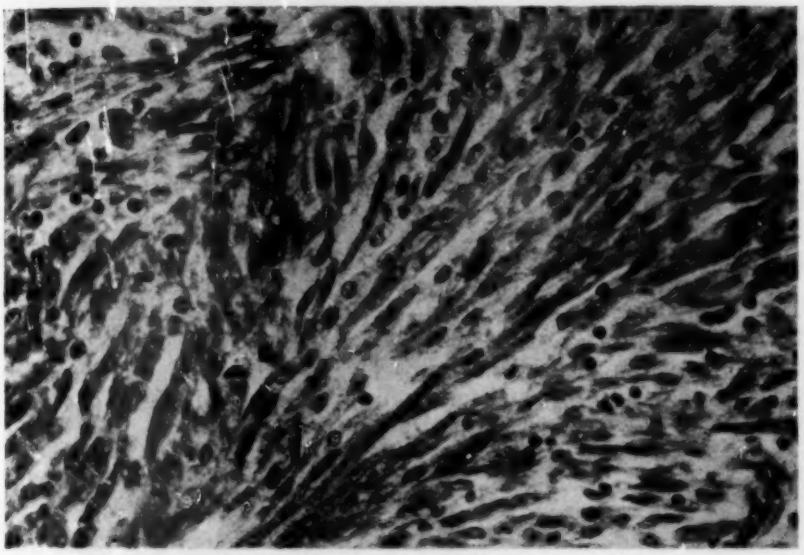

Fig. 3.—The morphologic aspects of the neoplastic cells are clearly shown in this photomicrograph. Note the variation from bluntly ovoid to extremely elongated forms with centrally located vesicular nuclei. Masson trichrome stain; × 400.

The lung parenchyma surrounding the tumor was compressed, and in some areas neoplastic cells partially filled alveolar spaces. The neoplasm for the most part, however, was encapsulated by irregular but dense collagenic tissue.

COMMENT

A pulmonary lesion described by Rosendahl [7] as diffuse myomatosis of the lungs is not to be confused with the solitary smooth muscle tumors, such as the one reported here.

Rosendahl's lesion and those described by von Stoessel,[8] Berg and Vejlens [9] and Berg and Zachrisson [10] represent a myomatous transfor-

7. Rosendahl, T.: Acta radiol. **23**:138, 1941.

(Footnotes continued on next page)

mation of pulmonary tissue surrounding alveobronchiolar cavities, which for the greater part are highly distended. The genesis of this condition, if not neoplastic, has been attributed by von Stoessel, as a sequela, to chronic inflammation. This view, however, is not supported by the other authors mentioned. Necropsy in the cases reported by Berg and Vejlens and Berg and Zachrisson revealed tuberous sclerosis of the brain, and these authors associated the smooth muscle lesions with the complex seen in tuberous sclerosis.

Rosendahl did not accept either of these views and left the question of genesis entirely open.

As for those lesions which are solitary and intimately associated with the larger bronchial structures, there is no reason to doubt their neoplastic nature. In the patient studied by us respiratory symptoms first developed three years prior to death, and the progression of the tumor was followed by repeated roentgen studies over a period of approximately one year. The symptoms and the physical findings were those of bronchial occlusion due to neoplasm and suggested, along with the roentgen findings, bronchiogenic carcinoma.

The location of the tumor, with its involvement of the coryna, precluded surgical cure of the neoplasm. There was a reasonable chance, however, that extirpation of the lung and the tumor would prevent further hemorrhages and that even if a small amount of tumor tissue was left in the main bronchus the patient's life might be prolonged.

If the neoplasm had been proved to be a bronchiogenic carcinoma, a palliative operation would not have been recommended. In this case, however, tissue obtained through the bronchoscope demonstrated a low grade leiomyosarcoma. There was no possibility of favorable effects from roentgen therapy, and serious hemoptysis could not be controlled by any other means than surgical intervention.

SUMMARY

A 34 year old Negro man had a primary leiomyosarcoma of the right upper lobe bronchus. The tumor was diagnosed histologically before pneumonectomy was attempted. Six other cases of a mesenchymal neoplasm of bronchial origin of this type have been recorded in the literature.

W. S. R.—Watts Hospital, Durham, N. C.
B. B.—1335 H Street, Washington, D. C.

8. von Stoessel, E.: Beitr. z. Klin. d. Tuberk. **90**:432, 1937.
9. Berg, G., and Vejlens, G.: Acta pædiat. **26**:16, 1939.
10. Berg, G., and Zachrisson, C. G.: Acta radiol. **22**:425, 1941.

GLOMERULONEPHRITIS, WILMS'S TUMOR AND HORSESHOE KIDNEY IN AN INFANT

NATHAN J. SMITH, M.D., MINNEAPOLIS

THIS case is presented because of the unusual clinical picture and the interesting findings at autopsy.

A 10 month old boy was referred to the University Hospitals because of a large mass in the abdomen. Since 3 months of age he had had many infections of the respiratory tract. In spite of these, he had taken feedings well and developed normally. One month prior to his admission his mother noted that the left side of the abdomen was distended. There was concurrently a loss of appetite as well as irritability. Sulfadiazine was prescribed for a period of two days. One week prior to his admission, swelling about the face, the scrotum and the legs was noted, and the mother felt a large, firm mass in the abdomen. The child was taken to a urologist, who made the diagnosis of Wilms's tumor and recommended that the child be admitted to the hospital.

All other aspects of the history were entirely irrelative. The child represented the mother's second normal pregnancy, and the neonatal period had been free of complications.

Physical Examination.—The patient's temperature was 98.6 F. (rectum). The body weight was 9.12 Kg. The child appeared to be irritable but in no acute distress. The circumference of the head was 46 cm., and the fontanels were closed. Edema of the face was present, being most marked about the eyelids. The pupils were round and equal, reacting well to light. Slight convergent strabismus was present on the right side. The fundi were thought to show some generalized edema, most marked near the optic disk. The pharyngeal mucous membrane was slightly hyperemic. Some discrete small anterior cervical lymph nodes were palpable on the right side. The heart and the lungs were thought to be normal. The abdomen was distended but not noticeably tender. A large mass, which was firm, immovable and somewhat irregular, was palpable in the left side of the abdomen. It occupied the entire left portion of the abdominal cavity from the costal margin to the pelvis and from the midline to the lateral abdominal wall. Percussion revealed a slightly tympanitic note over the right side of the abdomen; the left side gave a sound that was flat to dull. There were no changes in the findings with changes in position. Several small soft nodes were palpable in the inguinal regions bilaterally. Both testes were felt in the scrotum, which was noticeably edematous. The extremities appeared edematous, especially over the lower parts of both legs, where moderate pitting edema was found. Neurologic examination disclosed no abnormality.

Several examiners attempted to determine the blood pressure on repeated occasions. A small cuff was used, but there was failure to obliterate the radial pulse at a pressure of 300 mm. of mercury.

From the Department of Pathology, University of Minnesota.

The specific gravity of the urine was 1.023; the p_H value was 5. The urine contained albumin (3 plus); occasional leukocytes and finely granular casts were also present. A routine study of the blood revealed 11.2 Gm. of hemoglobin per hundred cubic centimeters and 16,400 leukocytes per cubic millimeter, of which 52 per cent were neutrophils, 39 per cent lymphocytes, 5 per cent monocytes, 2 per cent eosinophils and 2 per cent basophils.

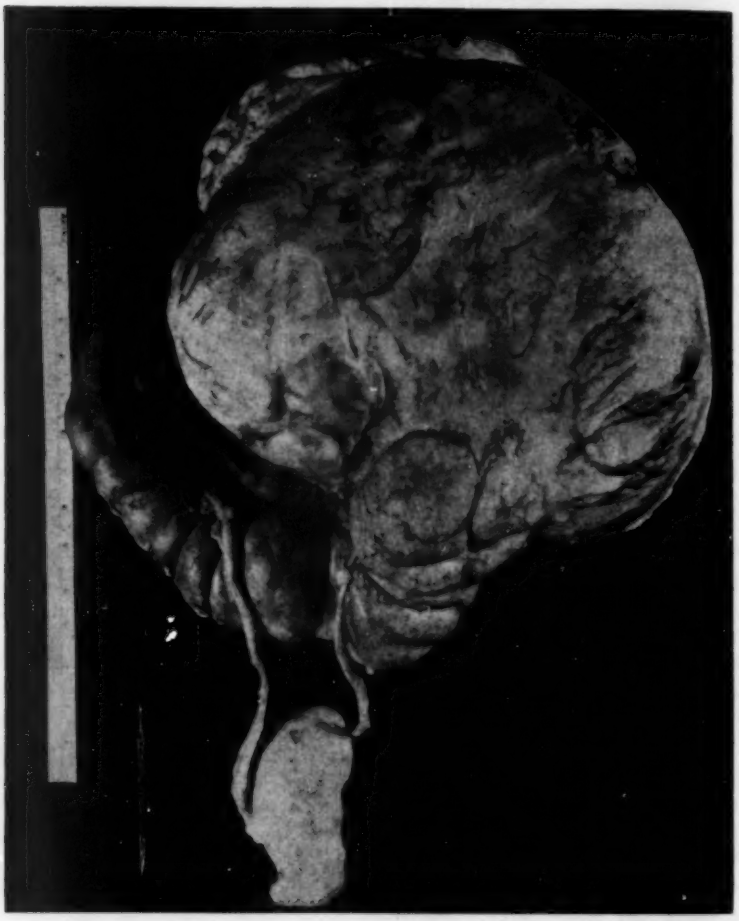

Fig. 1.—The tumor mass removed from a 10 month old boy who suffered from edema, hypoproteinemia, hypercholesteremia, albuminuria and severe hypertension.

Three days prior to the patient's admission roentgen studies had been done at the referring hospital to determine further the nature of the abdominal mass. A barium sulfate enema showed the colon displaced to the right by a large homogeneous soft tissue mass in the upper left region of the abdomen. As the splenic flexure was not depressed, the possibility of an enlarged spleen was

excluded. A gastrointestinal roentgen series showed the stomach and the small bowel displaced to the right.

Clinical Course.—The patient was given a diet of purees suitable to a baby and routine pediatric care. He was prepared for intravenous urographic examination which was attempted on his second hospital day. This examination was unsatisfactory. A large mass was seen which apparently was in the posterior region of the abdomen, appearing to be identical with the kidney on the left side. A roentgenogram of the chest revealed a left ventricular type of cardiac enlargement.

The third day the child was noted to be more edematous and to have clinically demonstrable ascites. He had gained 0.43 Kg. in weight since admission. The blood urea nitrogen was 50 mg., the blood cholesterol 676 mg. and the plasma proteins 3.8 Gm. per hundred cubic centimeters.

The patient continued to show increasing edema and ascites so that by the sixth hospital day his weight had increased 0.53 Kg. more and by the eighth day 0.50 Kg. more. Active treatment was limited to supportive measures, including a transfusion of 150 cc. of whole blood on the sixth day; two days later 80 cc. was given. The edema was progressive, and on the ninth hospital day an attempt was made to replace plasma proteins with concentrated plasma, 50 cc. being given. Soon after this was administered, the patient became cyanotic and dyspneic. Numerous moist rales were heard over the entire chest. A diagnosis of cardiac decompensation was made and the infant placed in an oxygen tent. It was decided to digitalize the patient, and digalen, 0.25 cat unit (0.5 cc.), was given intravenously. These measures failed to ameliorate the child's condition in any way, and the patient died on the evening of the ninth hospital day.

Autopsy.—The right pleural cavity contained 75 cc., and the left 100 cc., of clear yellow fluid. The lungs showed hypostatic congestion and edema. The heart was enlarged, with moderate dilatation of the right atrium. The transverse diameter of the heart was 8.3 cm. The intrathoracic diameter of the chest was 15 cm. Hypertrophy of the left ventricular wall was observed, with the myocardium measuring 1.10 cm. in thickness at the apex.

A large retroperitoneal mass occupied most of the abdominal cavity on the left, displacing the small intestine and the stomach to the right. It was found to originate from the upper pole of the left kidney and measured 14 by 5 by 6.5 cm. (fig. 1). It was grayish yellow and had a somewhat irregular surface. Microscopic sections were made from a number of different parts of the tumor. Over 90 per cent of the tissue was necrotic, but there were numerous islands of living tumor tissue. The necrotic tissue consisted largely of shadows of striated muscle fibers. The non-necrotic portions consisted chiefly of adult striated muscle fibers, but there were occasional areas of undifferentiated muscle, and a few tubules were found such as occur in adenosarcoma. The diagnosis was therefore Wilms's tumor (rhabdomyosarcoma).

The kidneys were united in the midline anterior to the vertebral bodies, presenting a typical horseshoe deformity. The left kidney measured 7 by 3 by 2.5 cm. and the right 8.5 by 3 by 2.7 cm. There was fetal lobulation. Several small cysts, measuring 0.2 to 1.0 cm. in diameter, were visible. On section the cortex was found to be 8 mm. in thickness. The cortical tissue was yellow, but the medulla showed no abnormality. The cysts were confined to a few small subcapsular areas in the cortex. The ureter and the bladder were normal.

The brain was examined grossly and sectioned. There were no demonstrable lesions.

Microscopically, the following changes were evident. Under low magnification it was noted that there was moderate diffuse tubular atrophy (fig. 2). The glomeruli all showed endothelial proliferation of some degree with capillary obstruction, which was responsible for the tubular atrophy. Many of the glomeruli showed epithelial crescents, which were partly fibrous, as shown in figure 2. This is a characteristic picture of subacute glomerulonephritis.

COMMENT

The abdominal mass, edema, albuminuria, hypercholesteremia, severe hypertension and renal insufficiency constitute a most challenging clinical picture. The large retroperitoneal tumor apparently arising from the left kidney would make probable the clinical diagnosis of Wilms's tumor.

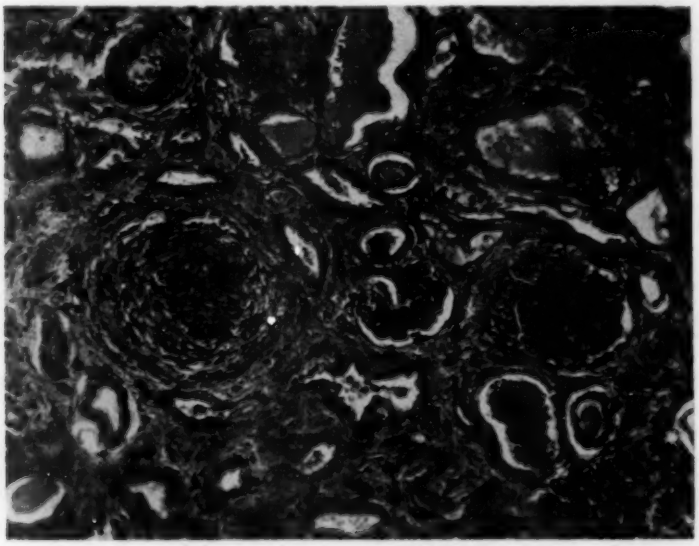

Fig. 2.—Photomicrograph of kidney.

All the aspects of this case certainly could not be explained on the basis of this neoplasm alone.

It is now recognized that hypertension may occur in a child with Wilms's tumor. Bradley and Pincoff [1] have observed 5 consecutive patients with this tumor, all having arterial hypertension. In 2 patients removal of the tumor reduced the blood pressure to normal. Daniel [2] studied 18 patients, ranging in age from 8 months to 9 years; in all but 4 there was definite hypertension. These 4 patients were the only ones who were free of recurrence or metastasis at the time of the author's report. The highest pressure recorded in this series was 164 systolic

1. Bradley, J. E., and Pincoff, M. C.: Ann. Int. Med. **2**:1613, 1938.
2. Daniel, W. E.: South. M. J. **32**:104, 1939.

and 130 diastolic. Braasch, Walters and Hammer [3] also studied 18 patients and found hypertension in only 5. Koons and Ruch [4] removed a Wilms tumor from a 7 year old girl whose blood pressure was 180 systolic and 130 diastolic, and eleven days later the blood pressure had fallen to 116 systolic and 76 diastolic.

It is evident therefore that Wilms's tumor can produce hypertension. The mechanism involved in this is not known. Daniel [2] expressed the belief that the relative renal ischemia is the causative factor. Bradley and Pincoff [1] postulated that pressor substances secreted by the tumor tissue were responsible. Their analysis of one Wilms tumor removed from a child with hypertension revealed that such substances were not present. In no case reported has there been a degree of hypertension simulating that found in the case studied here. It appears unlikely that Wilms's tumor alone could cause such extreme elevation of the blood pressure as was observed in this 10 month old infant. One must conclude that other factors were present to explain not only this but other aspects of the case.

The presence of glomerulonephritis in an infant under 1 year of age is not common.[5] Albuminuria, hypertension and uremia with absence of hematuria, may at times be found when this condition occurs during childhood. The extensive glomerular damage observed in the infant studied can certainly be regarded as sufficient to explain the definite albuminuria and the uremia and may constitute the major factor in the production of the hypertension.

Finding two relatively uncommon pathologic conditions in an organ also having congenital malformation, namely, a horseshoe kidney, is an extremely rare clinical event. The horseshoe kidney has been reported observed at a rate varying from 1 in 385 autopsies (Shoemaker and Braasch) to 1 in 1,000 (Davidsohn). Eliason and Stevens [6] have provided the one report in the literature of Wilms's tumor arising in a horseshoe kidney. No report could be found, however, in which these two conditions were described to occur complicated by the presence of glomerulonephritis.

The cardiac involvement in this case deserves brief mention, as it doubtless was the primary factor in the terminal episode. Wessler [5] in 1914 drew attention to the cardiac changes in nephritis in children. He observed hypertrophy of the left ventricle with both acute and chronic glomerulonephritis and emphasized that such changes might develop in the relatively short period of a few weeks. Left ventricular hypertrophy was found to be present in the case reported here to the extent that might be found in classic hypertensive heart disease in the adult. Failure of the left side of the heart was the immediate cause of death. The progress

3. Braasch, W. F.; Walters, W., and Hammer, H. J.: J. A. M. A. **115:** 1837, 1940.

4. Koons, K. M., and Ruch, M. K.: J. A. M. A. **115:**1097, 1940.

5. Wessler, H.: Arch. Int. Med. **14:**517, 1914.

6. Eliason, E. L., and Stevens, L. W.: Ann. Surg. **119:**788, 1944.

of the terminal events would indicate that the failure of the heart was precipitated by the increase in the volume of blood following the administration of concentrated plasma. Rubin [7] has reported two deaths in children with nephritis to whom a 50 per cent dextrose solution had been given intravenously as a diuretic.

SUMMARY

A 10 month old infant had progressive edema, an abdominal mass, severe hypertension, albuminuria, hypoproteinemia and definite hypercholesteremia. An autopsy revealed subacute glomerulonephritis, Wilms's tumor and horseshoe kidney.

7. Rubin, M. I., in Nelson, W. E.: Mitchell-Nelson Textbook of Pediatrics, ed. 4, Philadelphia, W. B. Saunders Company, 1945.

Books Received

RENAL DISEASES. By E. T. Bell, M.D., professor of pathology in the University of Minnesota, Minneapolis. Pp. 434, with 115 engravings and 4 color plates. Price $7. Philadelphia: Lea & Febiger, 1946.

This monograph is, according to the author's preface, "in part a compilation of studies on renal disease carried on by the author during the past twenty-five years." Much of the subject matter has been published in various journals, particularly in the *American Journal of Pathology* and the ARCHIVES OF PATHOLOGY. But this new volume is far from being merely a compilation or a reprinting of old material. It is a complete, well integrated presentation of diseases of the kidneys from the point of view of structural pathology, with a discussion of the correlated pathologic physiologic aspects and clinical manifestations.

These studies are based on an analysis of all the cases of diseases of the kidneys mentioned in the records of 32,360 autopsies. Since the subjects of these autopsies were derived from a large number of hospitals of all types—educational, charity and privately owned—and the number of cases of diseases of the kidneys is so large, deductions concerning the relative incidence of the various types of renal disease are statistically significant.

The book is divided into twelve chapters. The first chapter is a short classification of renal diseases. The second presents the normal histology, and the third the normal and the pathologic physiology, of the kidneys. These are followed by chapters on: developmental anomalies; obstructions of the urinary tract—hydronephrosis; glomerulonephritis; tubular disease; acute interstitial nephritis (pyelonephritis); diseases of the blood vessels; diseases of the kidneys related to metabolic disturbances; extrarenal azotemia; tumors of the kidneys. The volume is well and copiously illustrated with 115 charts, photographs of gross specimens and photomicrographs, including four colored plates. The cases in each group and subgroup of diseases are tabulated in a manner that facilitates study and analysis; there are 73 tables. Each subdivision is followed by an excellent bibliography pertaining to its particular subject. At the end is an adequate index of 6 pages. The author writes with admirable clearness, without decoration and without dulness.

This monograph illustrates the modern concept of pathology and its place in medicine, namely, that the structural changes induced in an organ by disease furnish the soundest basis for an understanding of the functional disturbances that result from disease. The entire volume will interest all pathologists. Large sections of it will prove useful to practitioners of such diverse specialties as internal medicine and urology. Even obstetricians will find much instruction in the section of 21 pages on the toxemias of pregnancy, based on a study of 52 cases that were examined at autopsy. The work can be recommended as a comprehensive and illuminating discussion of all phases of the diseases that occur in that interesting and essential pair of organs, the kidneys.

MONGOLISM AND CRETINISM: A STUDY OF THE CLINICAL MANIFESTATIONS AND THE GENERAL PATHOLOGY OF PITUITARY AND THYROID DEFICIENCY. By Clemens E. Benda, M.D., director, Wallace Research Laboratory for the Study of Mental Deficiency, Wrentham, Mass., and instructor in neuropathology, Harvard Medical School. Price $6.50. Pp. 310, with 110 illustrations. New York: Grune and Stratton, 1946.

The essential purpose of this book is to advance the knowledge and understanding of mongolism, which is the most frequent disorder of growth of infancy. It is estimated that there are 60,000 mongoloid persons in the United States and

that, of the 8,650 human beings born daily, 17 are probably mongoloid. The results of a study of mongolism as observed during ten years in some 300 persons of all ages from 2 days to 30 years, including 50 on whom autopsies were done, are analyzed and discussed. It is assumed that "in the mongoloid, nature has provided mankind with one of her strangest experiments—creating a human being without proper function of the pituitary," and the nature of the functional disturbance is not known. Features of cretinism are included in the presentation in order that this as yet poorly understood complicated disorder of growth may be compared with the disorder of growth caused by a single gland. Mongolism and cretinism are considered separately in the same chapters. After the historical introduction —mongolism was described first in 1866—come chapters on the physical characteristics and the diagnosis, the mental development, the nervous system, the morphologic changes in the endocrine glands, as well as those in other organs, the growth of the skeleton (especially that of the skull) and the results of roentgenologic, hematologic and biochemical examinations. The final chapters discuss the relation of the maternal condition to mongolism, the possibilities of its prevention, and its treatment. There is an author and subject index. Each chapter is provided with a comprehensive bibliography. There are 48 tabulations as well as numerous condensed clinical histories and descriptions of pituitary, thyroid and adrenal glands. The morphologic aspects on the whole are well illustrated, but one wishes that the pituitary gland of the mongoloid could have been more thoroughly studied and more clearly pictured. The book is an important contribution to the study of mongolism and should mark the beginning of comprehensively organized efforts to solve the problems of its causation and prevention.

LES TUMEURS ET LES POLYPES DU COEUR: ETUDE ANATOMO-CLINIQUE. By Dr. Ivan Mahaim. Preface by Prof. Dr. Jean-Louis Nicod. Monograph of the Institute of Pathologic Anatomy of the University of Lausanne. Pp. 568, with 67 illustrations. Paris: Masson & Cie [Lausanne: F. Roth & Cie], 1945.

The author, a Swiss cardiologist of standing, is perhaps best known for his writings on the His-Tawara system. His present monograph is based on an exhaustive review of the literature and on a series of thorough personal observations. The first part of the book deals with the neoplastic and thrombotic polypoid formations of the heart, their anatomy, locations and effects, their diagnosis and the possibilities of surgical treatment. The details of 250 reported cases of auricular polypi are tabulated; the most frequent polypi are the myxomatous ones. The second and third parts concern the nonpolypoid benign tumors and the cancers of the heart, rsepectively. Celothelioma or mesothelioma of the node of Tawara—Mönckeberg's lymphangioendothelioma—receives special consideration, and a case observed by the author is described in detail and well illustrated. The main details of 87 instances of primary sarcoma of the heart are given in tabular form. Some 115 pages are devoted to the secondary tumors of the heart. Several cases studied with special reference to diagnosis by the author are recorded, and the bibliography of cardiac metastases is analyzed with respect to the origins of these. The fourth part discusses the tumors of the pericardium, and here again special stress is placed on diagnosis and treatment. The "general conclusions" review fundamental problems of diagnosis and the question of surgical treatment of cardiac tumors and polyps. A table lists 28 cases—2 original—in which a positive clinical diagnosis of cardiac tumor was made. A strong plea is made for great care in the etiologic diagnosis of cardiac insufficiency. The gross appearances of cardiac tumors are well illustrated. The bibliography lists 1,298 references. There is a table of the case reports in the text, and there are complete author and subject indexes. The book is a great storehouse of information about cardiac tumors and polyps and, as emphasized by Professor Nicod in its preface, it prepares the way for the expansion of cardiac surgery.